

Exhibit 29

Confidential Subject to Protective Order

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: ACETAMINOPHEN -) MDL No. 3043
ASD-ADHD PRODUCTS)
LIABILITY LITIGATION) Case No.
_____) 1:22-md-03043-DLC
)
THIS DOCUMENT RELATES TO:) JUDGE DENISE
All Cases) COTE
_____)

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

— — —
Friday, September 8, 2023
— — —

Video-Recorded Oral Deposition of
MITCHELL R. MCGILL PhD held at the offices of
Quattlebaum Grooms & Tull PLLC, 111 Center
Street, Suite 1900, Little Rock, Arkansas,
commencing at 8:46 a.m. CDT on the above
date, before Michael E. Miller, Fellow of the
Academy of Professional Reporters, Certified
Court Reporter, Registered Diplomate
Reporter, Certified Realtime Reporter and
Notary Public.

— — —
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1 -----

2 P R O C E E D I N G S

3 September 8, 2023, 8:46 a.m. CDT

4 -----

5 THE VIDEOGRAPHER: We are now

6 on the record. My name is Dan Lawlor.

7 I'm the videographer representing

8 Golkow Litigation Services.

9 Today's date is September 8th,

10 2023, and the time is 8:46 a.m.

11 This video deposition is being

12 held in Little Rock, Arkansas in the

13 matter of Acetaminophen Tylenol

14 ASD-ADHD Products Liability

15 Litigation, MDL No. 3043.

16 The deponent is Mitchell

17 McGill.

18 Counsel will be noted on the

19 stenographic record.

20 The court reporter is Mike

21 Miller and will now swear in the

22 witness.

23 ///

24 ///

25 ///

Page 16

1 -----

2 MITCHELL R. MCGILL PhD,

3 having been duly sworn,

4 testified as follows:

5 -----

6 EXAMINATION

7 -----

8 BY MR. JANUSH:

9 Q. Good morning, Dr. McGill.

10 A. Good morning.

11 Q. Dr. McGill, in 2013, you

12 received your doctorate in toxicology from

13 the University of Kansas Medical Center; is

14 that right?

15 A. That's correct.

16 Q. And you are not a neurologist;

17 is that correct?

18 A. I'm not.

19 Q. And you are not an

20 epidemiologist, true?

21 A. I am not an epidemiologist.

22 Q. And you're not a medical

23 doctor, right?

24 A. I am a PhD.

25 Q. But you're not a medical

Page 17

1 doctor, right?

2 A. Correct.

3 Q. Okay. And aside from a review

4 article you wrote with your wife, have you

5 ever actually studied autism, the disease

6 state?

7 MR. COHEN: Objection to the

8 form.

9 A. Aside from that article, I have

10 not done original research on the subject of

11 autism.

12 BY MR. JANUSH:

13 Q. Okay. And that article wasn't

14 original research either, right? It was a

15 review of articles, right?

16 A. It's a narrative review of the

17 literature. When we write a review like

18 that, we try to review as much of the

19 relevant literature as we possibly can and

20 evaluate it critically so there is original

21 analysis.

22 Q. But it's original analysis of

23 other people's publications, right?

24 A. It's original analysis of prior

25 studies that have been performed by others.

<p>Page 18</p> <p>1 Q. Okay. And have you ever 2 studied ADHD before?</p> <p>3 A. Aside from what we mentioned 4 about it in that review article, I have not 5 done original research on ADHD.</p> <p>6 Q. Do you have any experience 7 publishing in the field of developmental 8 neurotoxicity or DNT?</p> <p>9 A. I don't believe I've published 10 any original research articles in that area.</p> <p>11 Q. Do you have experience -- well, 12 you're not a teratologist either, right?</p> <p>13 A. My expertise is not in 14 teratology. Teratology could be considered a 15 component of toxicology, and I am a 16 toxicologist.</p> <p>17 Q. But you're not a teratologist, 18 right?</p> <p>19 MR. COHEN: Objection, asked 20 and answered.</p> <p>21 A. Well, again, teratology is -- 22 could be considered sort of a subfield of 23 toxicology, so I'm trained as a toxicologist. 24 I don't do -- I don't do original research on 25 the -- what would widely be considered</p>	<p>Page 20</p> <p>1 Q. Are you an expert on the fetal 2 brain? I'm not asking about acetaminophen. 3 Are you an expert on the fetal brain?</p> <p>4 MR. COHEN: Object to the form.</p> <p>5 A. The "fetal brain" is a rather 6 broad topic. Again, I'm an expert on 7 acetaminophen metabolism, and I think that's 8 relevant to the question at hand here of 9 whether or not acetaminophen can be converted 10 to NAPQI within the fetal brain.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. I appreciate that you'd like to 13 determine what's relevant, but for the 14 moment, I'm going to be asking the questions 15 and you're going to be answering them or it's 16 going to be a very long day.</p> <p>17 So I'm just asking: Are you an 18 expert on the fetal brain? I'm not talking 19 about acetaminophen. We're not talking about 20 your assignment or reason you're here today.</p> <p>21 Are you an expert on the fetal 22 brain?</p> <p>23 MR. COHEN: Object to the form. 24 I don't think it's appropriate to 25 lecture the witness on his role.</p>
<p>Page 19</p> <p>1 teratology. 2 BY MR. JANUSH:</p> <p>3 Q. In any bios that you have 4 online, within your university, LinkedIn or 5 otherwise, do you hold yourself out to others 6 as a teratologist?</p> <p>7 A. I don't believe so, no.</p> <p>8 Q. Are you an expert on the fetal 9 brain?</p> <p>10 A. I'm an expert on the subject of 11 acetaminophen metabolism, and the questions 12 at hand here are about acetaminophen 13 metabolism in the brain, particularly the 14 fetal brain, after maternal ingestion of 15 therapeutic doses of acetaminophen. So in 16 that sense, I'm an expert on this subject 17 matter.</p> <p>18 MR. JANUSH: Move to strike as 19 nonresponsive.</p> <p>20 BY MR. JANUSH:</p> <p>21 Q. Do you remember my question? 22 MR. COHEN: Object to the form. 23 MR. JANUSH: I asked a simple 24 question. 25 BY MR. JANUSH:</p>	<p>Page 21</p> <p>1 MR. JANUSH: Well, I've asked 2 it twice already. I'm not getting an 3 answer to the very straightforward 4 question. It has one, two, three, 5 four, five, six, seven, eight words. 6 Eight words.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. Are you an expert on the fetal 9 brain? That's all I'm asking.</p> <p>10 MR. COHEN: Object to the form.</p> <p>11 A. The words are fairly broad, as 12 I stated. Again, I'm an expert in 13 acetaminophen metabolism, and the question at 14 hand here is whether or not the fetal brain 15 is metabolized to form -- excuse me, can 16 metabolize acetaminophen to form NAPQI, and 17 as an expert in acetaminophen metabolism, I'm 18 qualified to comment on that.</p> <p>19 BY MR. JANUSH:</p> <p>20 Q. I didn't ask you that. Do you 21 understand that?</p> <p>22 MR. COHEN: Object to the form.</p> <p>23 BY MR. JANUSH:</p> <p>24 Q. I'm not asking you what you're 25 qualified to comment on with respect to</p>

<p style="text-align: right;">Page 22</p> <p>1 today's assignment or the reason you're here</p> <p>2 today. I'm only asking if you're an expert</p> <p>3 on the fetal brain.</p> <p>4 MR. COHEN: Object to the form.</p> <p>5 BY MR. JANUSH:</p> <p>6 Q. Let me ask it differently:</p> <p>7 What have you published on the fetal brain?</p> <p>8 A. Aside from what we've discussed</p> <p>9 in that review that again involved critical</p> <p>10 analysis and evaluation of the literature</p> <p>11 that is relevant to that, I've not published</p> <p>12 original research articles dealing with the</p> <p>13 fetal brain.</p> <p>14 Q. So as someone who has never</p> <p>15 published original research articles dealing</p> <p>16 with the fetal brain, do you hold yourself</p> <p>17 out as an expert on the fetal brain?</p> <p>18 A. Again, I don't feel that that</p> <p>19 can be answered with a yes or a no. I've</p> <p>20 given my answer, and I'll probably just</p> <p>21 repeat it again, which is that I'm an expert</p> <p>22 in acetaminophen metabolism, and I can speak</p> <p>23 to that in the fetal brain.</p> <p>24 Q. You understand that this</p> <p>25 transcript is going to be appended to</p>	<p style="text-align: right;">Page 24</p> <p>1 court's order and that limitation, but</p> <p>2 when an attorney, an opposing</p> <p>3 attorney, is --</p> <p>4 MR. JANUSH: You don't have to</p> <p>5 give a speech.</p> <p>6 MR. COHEN: Excuse me, let me</p> <p>7 finish. Is lecturing a witness on how</p> <p>8 a witness needs to answer his</p> <p>9 questions, that's outside the scope of</p> <p>10 that limitation.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. I didn't lecture. I asked if</p> <p>13 you understood that the judge is going to be</p> <p>14 reading this transcript.</p> <p>15 MR. COHEN: And that's a</p> <p>16 lecture. Just ask your questions.</p> <p>17 MR. JANUSH: And just say</p> <p>18 objection to form.</p> <p>19 MR. COHEN: Unless there's</p> <p>20 inappropriate conduct being conducted.</p> <p>21 MR. JANUSH: Just say objection</p> <p>22 to form or we will --</p> <p>23 MR. COHEN: Continue, Counsel.</p> <p>24 MR. JANUSH: Or we will mark</p> <p>25 this and file a motion literally by</p>
<p style="text-align: right;">Page 23</p> <p>1 briefing before a federal judge who's going</p> <p>2 to have the opportunity to read my questions</p> <p>3 and your answers, right?</p> <p>4 A. Yes.</p> <p>5 Q. Fair to say you want to be</p> <p>6 really responsive and accurate in response to</p> <p>7 my questions?</p> <p>8 MR. COHEN: Object to the form.</p> <p>9 You don't need to lecture the witness</p> <p>10 on his role --</p> <p>11 MR. JANUSH: You can only say</p> <p>12 object to the form, Counsel. That's</p> <p>13 warning number one. Object to the</p> <p>14 form --</p> <p>15 MR. COHEN: No.</p> <p>16 MR. JANUSH: That is the</p> <p>17 deposition protocol that I helped</p> <p>18 enter in this case on behalf of the</p> <p>19 plaintiffs, and I negotiated with the</p> <p>20 defendants' counsel, one of which was</p> <p>21 not you, and that is the order.</p> <p>22 "Object to form" are the only words</p> <p>23 you may use, period.</p> <p>24 MR. COHEN: With all due</p> <p>25 respect, Mr. Janush, I acknowledge the</p>	<p style="text-align: right;">Page 25</p> <p>1 Monday.</p> <p>2 MR. COHEN: You may continue.</p> <p>3 MR. JANUSH: Oh, I don't need</p> <p>4 your permission to continue, but I</p> <p>5 appreciate your courtesy.</p> <p>6 BY MR. JANUSH:</p> <p>7 Q. Are you a pharmacologist?</p> <p>8 A. My PhD is in toxicology, and</p> <p>9 the program in which I was trained, that</p> <p>10 required initial training in pharmacology and</p> <p>11 then additional classes in toxicology.</p> <p>12 Q. Are you a pharmacologist? I'm</p> <p>13 not talking about your training. Are you a</p> <p>14 pharmacologist?</p> <p>15 A. Again, I'm trained in</p> <p>16 pharmacology as part of my PhD training, part</p> <p>17 of my PhD coursework, so I have pharmacology</p> <p>18 training and I have additional training in</p> <p>19 toxicology.</p> <p>20 Q. Aside from your training, are</p> <p>21 you offering yourself in this case as an</p> <p>22 expert in pharmacology?</p> <p>23 A. I'm offering my help in this</p> <p>24 case as an expert in specifically</p> <p>25 acetaminophen metabolism and toxicity.</p>

<p style="text-align: right;">Page 26</p> <p>1 Q. So is that a no?</p> <p>2 A. I wouldn't call it a no.</p> <p>3 It's -- insofar as it is relevant to</p> <p>4 acetaminophen metabolism and toxicity, I can</p> <p>5 comment on the pharmacology.</p> <p>6 Q. I'm not asking what you can</p> <p>7 comment on. I asked if you're offering</p> <p>8 yourself as an expert in pharmacology.</p> <p>9 MR. COHEN: Object to the form.</p> <p>10 A. Again, I'm offering myself as</p> <p>11 an expert -- maybe I can restructure my</p> <p>12 response a little bit, if that would be</p> <p>13 helpful.</p> <p>14 I'm offering my services or my</p> <p>15 help or expert -- expertise in this case as</p> <p>16 an expert in acetaminophen metabolism and</p> <p>17 toxicity, and pharmacology insofar as it is</p> <p>18 relevant to those questions.</p> <p>19 BY MR. JANUSH:</p> <p>20 Q. Would you agree that in your</p> <p>21 report you devote a fair amount of your</p> <p>22 report to pharmacokinetics [sic]?</p> <p>23 A. Pharmacokinetics.</p> <p>24 Q. Sorry, yes, pharmacokinetics.</p> <p>25 A. Yes. Well, I specifically</p>	<p style="text-align: right;">Page 28</p> <p>1 heard the first part. Can you restate it?</p> <p>2 Q. Sure can.</p> <p>3 Historically, throughout your</p> <p>4 academic career and after receiving your</p> <p>5 doctorate in 2009, is it fair to say you have</p> <p>6 primarily been looking into the issue of</p> <p>7 liver damage arising from acetaminophen use?</p> <p>8 A. Most of my studies have focused</p> <p>9 on -- on the -- on acetaminophen</p> <p>10 hepatotoxicity. However, we've also done</p> <p>11 research on acetaminophen metabolism and</p> <p>12 toxicity in the cochlea, which is part of the</p> <p>13 auditory nervous system, as well as in the</p> <p>14 lung.</p> <p>15 Q. Right. And the cochlea was one</p> <p>16 study, correct?</p> <p>17 A. Actually --</p> <p>18 Q. One published piece of</p> <p>19 literature.</p> <p>20 A. Actually, three published</p> <p>21 pieces of literature. So one was looking</p> <p>22 at -- it was published -- I forget the year,</p> <p>23 I'm sorry, at the moment. But it was on the</p> <p>24 subject of -- what we did in that study was</p> <p>25 we gave mice acetaminophen and we looked at</p>
<p style="text-align: right;">Page 27</p> <p>1 address the pharmacokinetics of</p> <p>2 acetaminophen.</p> <p>3 Q. You offer criticisms of the</p> <p>4 opinions proffered by Dr. Louie, who actually</p> <p>5 is a pharmacologist; is that right?</p> <p>6 MR. COHEN: Objection to form.</p> <p>7 A. I'm -- criticisms with respect</p> <p>8 to what? With respect to pharmacokinetics?</p> <p>9 BY MR. JANUSH:</p> <p>10 Q. I'm just addressing that in</p> <p>11 your report you criticized Dr. Louie, who</p> <p>12 actually is a pharmacologist, true?</p> <p>13 MR. COHEN: Object to the form.</p> <p>14 A. I'm not criticizing Dr. Louie</p> <p>15 himself. I'm criticizing some of the claims</p> <p>16 that he's made, critically evaluating some of</p> <p>17 the claims that he's made.</p> <p>18 BY MR. JANUSH:</p> <p>19 Q. Historically, Dr. McGill,</p> <p>20 throughout your academic career and after</p> <p>21 receiving your doctorate in 2009, is it fair</p> <p>22 to say that you've primarily been looking</p> <p>23 into liver damage arising from acetaminophen</p> <p>24 use?</p> <p>25 A. I just want to make sure I</p>	<p style="text-align: right;">Page 29</p> <p>1 whether or not it causes, number one, hearing</p> <p>2 loss; number two, whether or not there's</p> <p>3 acetaminophen-protein adducts or glutathione</p> <p>4 depletion as surrogate markers of NAPQI</p> <p>5 formation.</p> <p>6 Another original study was on</p> <p>7 whether or not P450s are expressed in the</p> <p>8 cochlea, especially compared to the liver,</p> <p>9 and although we -- and we -- and the</p> <p>10 discussion of that, we addressed the</p> <p>11 implications for acetaminophen.</p> <p>12 And then the third was the</p> <p>13 review that we've discussed.</p> <p>14 Q. Sure.</p> <p>15 How many total publications</p> <p>16 concerning acetaminophen have you published</p> <p>17 approximately?</p> <p>18 A. I don't recall the exact</p> <p>19 number, but approximately -- I think it's</p> <p>20 around 75.</p> <p>21 Q. And so you just ticked off like</p> <p>22 four studies out of 75 that didn't have to do</p> <p>23 with acetaminophen use specifically</p> <p>24 associated with liver damage, right?</p> <p>25 MR. COHEN: Object to the form.</p>

<p style="text-align: right;">Page 30</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. In other words, out of</p> <p>3 approximately 75 studies, four of your</p> <p>4 studies didn't have to do with liver damage,</p> <p>5 right?</p> <p>6 A. It's hard for me to say without</p> <p>7 seeing the list --</p> <p>8 Q. Approximately. Try to move</p> <p>9 this along so we don't have to spend a lot of</p> <p>10 time on prefatory background.</p> <p>11 MR. COHEN: Object to the --</p> <p>12 object to the statement.</p> <p>13 Go ahead.</p> <p>14 A. My concern about the way you're</p> <p>15 phrasing the question is that counting number</p> <p>16 of publications is a valid way to assess</p> <p>17 somebody's expertise in an area.</p> <p>18 MR. JANUSH: Move to strike,</p> <p>19 nonresponsive. Not what I asked.</p> <p>20 MR. COHEN: I'm sorry, he</p> <p>21 wasn't even finished. Please don't</p> <p>22 interrupt the witness.</p> <p>23 A. I think, you know, there are</p> <p>24 other factors to consider.</p> <p>25 ///</p>	<p style="text-align: right;">Page 32</p> <p>1 question.</p> <p>2 MR. COHEN: Okay.</p> <p>3 BY MR. JANUSH:</p> <p>4 Q. Do you understand me?</p> <p>5 MR. COHEN: I'm going to make</p> <p>6 an objection.</p> <p>7 MR. JANUSH: You can, but this</p> <p>8 is -- I have made my record and I</p> <p>9 don't need to say more. I'm going to</p> <p>10 call the court if I can't get an</p> <p>11 answer.</p> <p>12 The witness does not get to</p> <p>13 make judgments in response -- if he</p> <p>14 doesn't like the question. That is</p> <p>15 not how this works.</p> <p>16 MR. COHEN: He --</p> <p>17 MR. JANUSH: You know it. So</p> <p>18 if you need to take a break, walk the</p> <p>19 witness out in the hall and give him</p> <p>20 some proper tutelage about how to</p> <p>21 answer deposition questions, I'm going</p> <p>22 to encourage you to do that.</p> <p>23 So I'm going to now, on the</p> <p>24 record, offer you that break before I</p> <p>25 take this further.</p>
<p style="text-align: right;">Page 31</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. Do you understand I'm only</p> <p>3 asking you, out of your total history of</p> <p>4 publishing scientific literature, what number</p> <p>5 of studies had nothing to do with liver</p> <p>6 damage?</p> <p>7 MR. COHEN: Object to the form.</p> <p>8 Go ahead.</p> <p>9 A. I understand your question. I</p> <p>10 think we've discussed that.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. I just want an answer.</p> <p>13 A. And my answer is I don't think</p> <p>14 that's an appropriate way to evaluate --</p> <p>15 counting papers is an appropriate way to</p> <p>16 evaluate expertise.</p> <p>17 Q. You don't get to -- you do not</p> <p>18 get to judge what is an appropriate way to</p> <p>19 evaluate anything today. I get to ask</p> <p>20 questions, and you have to answer my</p> <p>21 questions. And if you're not going to, I'm</p> <p>22 going to call Judge Cote and read this</p> <p>23 question and answer into the record and get a</p> <p>24 ruling within the next hour to cause you to</p> <p>25 actually listen to my question and answer my</p>	<p style="text-align: right;">Page 33</p> <p>1 MR. COHEN: He answered your</p> <p>2 question.</p> <p>3 MR. JANUSH: I'm going to offer</p> <p>4 you that break. Are you saying you</p> <p>5 don't want to take a break?</p> <p>6 MR. COHEN: I don't need to</p> <p>7 take a break.</p> <p>8 MR. JANUSH: Okay.</p> <p>9 BY MR. JANUSH:</p> <p>10 Q. My question was: Out of 75 --</p> <p>11 MR. COHEN: I'm just going to</p> <p>12 state for the record that I don't</p> <p>13 appreciate the lecturing to the</p> <p>14 witness.</p> <p>15 MR. JANUSH: Out of --</p> <p>16 MR. COHEN: Excuse me. Let me</p> <p>17 just finish at least; otherwise, we'll</p> <p>18 be talking over each other. He does</p> <p>19 not need to be lectured on how to be a</p> <p>20 witness.</p> <p>21 MR. JANUSH: He sure does.</p> <p>22 MR. COHEN: Your job is to ask</p> <p>23 questions.</p> <p>24 MR. JANUSH: And his job is to</p> <p>25 answer them. What I asked, not what</p>

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1 he wants to answer.

2 MR. COHEN: Maybe it's the

3 question, Counsel.

4 MR. JANUSH: The question is --

5 MR. COHEN: You're a capable --

6 MR. JANUSH: No more. No more.

7 MR. COHEN: No, no.

8 MR. JANUSH: David, no more.

9 MR. COHEN: You're a capable

10 lawyer.

11 MR. JANUSH: No more, David.

12 MR. COHEN: Rephrase your

13 question.

14 MR. JANUSH: No more.

15 BY MR. JANUSH:

16 Q. You've published approximately

17 75 pieces of scientific literature, true?

18 Yes or no?

19 A. No, I've published

20 approximately a hundred.

21 Q. A hundred --

22 A. I apologize, I need to rephrase

23 that. I published approximately 100

24 peer-reviewed published papers.

25 Q. Okay.

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1 A. In addition to that,

2 approximately a dozen textbook chapters.

3 Q. And of the approximate 100

4 peer-reviewed published papers, how many of

5 the approximate 100 had to do with liver and

6 acetaminophen?

7 A. I wasn't quite finished with my

8 answer.

9 So 100 peer-reviewed

10 manuscripts approximately. Approximately 12

11 book chapters that I can recall off the top

12 of my head, and somewhere in the range of 50

13 to 60 published abstracts.

14 Q. Now will you answer my

15 question?

16 A. Can you restate the question,

17 please.

18 Q. Of -- out of the total number

19 of publications you've published, how many

20 didn't have to do with the liver?

21 A. Including abstracts and book

22 chapters, I cannot recall the exact number.

23 It's more than four.

24 Q. Okay. Is this the first time

25 in your career testifying as an expert?

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1 A. Yes.

2 Q. Is this the first time you are

3 testifying in a deposition?

4 A. Yes.

5 Q. In this case, what entity is

6 your agreement with?

7 A. I don't recall having a written

8 agreement. I think my -- I think my

9 agreement is with Butler Snow.

10 Q. Okay. Do you understand which

11 corporate defendants you're working on behalf

12 of?

13 A. I'm aware of at least one of

14 them.

15 Q. And who is that?

16 A. The one that I'm aware of is

17 J&J.

18 Q. Okay. The maker and seller of

19 Tylenol, right?

20 A. In the United States.

21 Q. How did you come to serve as an

22 expert in this case?

23 A. I was sought by someone from

24 Butler Snow.

25 Q. Do you currently teach at the

Page 37

1 University of Alabama?

2 A. No.

3 Q. I mean of Arkansas. Sorry. I

4 meant to say Arkansas.

5 MR. WATTS: He's going to the

6 game.

7 MR. JANUSH: I'm going to

8 Alabama literally tonight, so forgive

9 me.

10 (Comments off the stenographic

11 record.)

12 THE WITNESS: You want to --

13 BY MR. JANUSH:

14 Q. Do you currently teach at the

15 University of Arkansas?

16 A. I teach at the University of

17 Arkansas for Medical Sciences.

18 Q. Okay.

19 A. Which is part of the University

20 of Arkansas system.

21 Q. What do you teach?

22 A. I teach -- so I teach PhD

23 students -- first of all -- well, there's two

24 different types of teaching, right. There's

25 formal classroom teaching and then there's

<p style="text-align: right;">Page 38</p> <p>1 mentorship, which is also a type of formal</p> <p>2 instruction. It's just practical hands on in</p> <p>3 the laboratory guiding through research. So</p> <p>4 I teach graduate students, PhD students in</p> <p>5 the lab through that mentorship type of</p> <p>6 teaching.</p> <p>7 I also lecture on drug</p> <p>8 metabolism and hepatotoxicity to graduate</p> <p>9 students. I also teach a course to public</p> <p>10 health students on -- currently teach a</p> <p>11 course to public health students on FDA</p> <p>12 regulations, and I also teach pathology</p> <p>13 residents, so primarily physicians in a</p> <p>14 pathology residency program, teach them</p> <p>15 clinical toxicology as well as a number of</p> <p>16 other subjects.</p> <p>17 Q. Are you a teacher that teaches</p> <p>18 like Monday to Friday?</p> <p>19 A. Monday through Friday? That</p> <p>20 kind of depends. That's a little bit hard to</p> <p>21 answer because some classes are online and</p> <p>22 asynchronous so they go technically</p> <p>23 throughout the day every week.</p> <p>24 In terms of physical, in-person</p> <p>25 lectures -- I'm sorry, I didn't know if I</p>	<p style="text-align: right;">Page 40</p> <p>1 A. Off the top of my head, I'm</p> <p>2 not -- could you produce the document so I</p> <p>3 can take a look at it, just in case</p> <p>4 there's --</p> <p>5 Q. I'm just asking if something --</p> <p>6 I don't want to spend a lot of time on this.</p> <p>7 I'm just asking if something comes to your</p> <p>8 mind that you've done that isn't addressed in</p> <p>9 your CV.</p> <p>10 A. Well, I'm trying to be</p> <p>11 cautious, you understand. As you mentioned,</p> <p>12 the judge will see this. I'm under oath. So</p> <p>13 I'd prefer to see a document.</p> <p>14 Q. That's okay. We'll move on.</p> <p>15 If it was accurate as of the date that you</p> <p>16 submitted your report, that's good enough for</p> <p>17 me.</p> <p>18 How did you prepare for today's</p> <p>19 deposition?</p> <p>20 A. So I wrote my report. In the</p> <p>21 process of writing my report, I reviewed a</p> <p>22 substantial amount of -- I reviewed the</p> <p>23 literature that you've seen, the materials</p> <p>24 for the case. So that was an enormous part</p> <p>25 of my preparation.</p>
<p style="text-align: right;">Page 39</p> <p>1 needed to pause.</p> <p>2 Q. I'm listening.</p> <p>3 A. In terms of in-person lectures,</p> <p>4 I teach -- so I teach the drug metabolism</p> <p>5 toxicity to PhD students in the spring, and</p> <p>6 then I teach pathology residents all</p> <p>7 throughout the year, but it's not necessarily</p> <p>8 every week. It's usually two to three days a</p> <p>9 week, and it may be one to two weeks a month</p> <p>10 typically.</p> <p>11 Q. Did you have an opportunity to</p> <p>12 review the CV, your résumé and appendices to</p> <p>13 your CV that was attached to your expert</p> <p>14 report?</p> <p>15 A. Yes.</p> <p>16 Q. Is it complete?</p> <p>17 A. Yes.</p> <p>18 Q. Any changes you need to make</p> <p>19 before we begin this deposition?</p> <p>20 A. Let me rephrase my prior</p> <p>21 answer. It's complete as of the date that's</p> <p>22 listed at the top of my CV.</p> <p>23 Q. Okay. What have you done since</p> <p>24 the date you submitted your expert report</p> <p>25 that would modify your CV?</p>	<p style="text-align: right;">Page 41</p> <p>1 Of course, my regular work and</p> <p>2 my career is -- some of it, at least, has</p> <p>3 relevance to the case, so I suppose you could</p> <p>4 consider that part of my preparation as well.</p> <p>5 I -- again, this is -- since</p> <p>6 this is the first time I'm doing a</p> <p>7 deposition, I have asked questions about how</p> <p>8 to conduct myself and things of that nature.</p> <p>9 Q. Who did you meet with to</p> <p>10 prepare for your deposition?</p> <p>11 A. Well, again, since part -- the</p> <p>12 greater part of my preparation for this</p> <p>13 deposition was in preparing my report and</p> <p>14 reviewing the literature, so the majority of</p> <p>15 that time was just me --</p> <p>16 Q. Did you meet with attorneys?</p> <p>17 A. I have met with counsel.</p> <p>18 Q. Who did you meet with?</p> <p>19 A. I met with Mr. Cohen,</p> <p>20 Ms. Lucas. I don't recall exactly. You</p> <p>21 know, some people I just met in passing.</p> <p>22 Q. On how many occasions did you</p> <p>23 meet with Mr. Cohen and Ms. Lucas?</p> <p>24 A. I don't recall the number.</p> <p>25 Q. More than ten?</p>

<p style="text-align: right;">Page 42</p> <p>1 A. I don't know. I don't recall 2 the number.</p> <p>3 Q. Can't give an answer at all, 4 like even if you were to estimate?</p> <p>5 A. Again, being under oath and as 6 you mentioned, the judge is watching -- will 7 watch this, I don't feel comfortable 8 answering without being certain.</p> <p>9 (Whereupon, Deposition 10 Exhibit P801, McGill Expert Report, 11 was marked for identification.)</p> <p>12 (Whereupon, Deposition 13 Exhibit P801B, McGill First 14 Supplemental Materials Reference List, 15 was marked for identification.)</p> <p>16 BY MR. JANUSH:</p> <p>17 Q. Dr. McGill, I'm going to hand 18 you what I'm marking as -- I've marked as 19 Plaintiffs' Exhibit 801 and 801B. 801 is 20 your report. 801B -- 801B is the addendum we 21 received yesterday, the supplemental 22 materials reference list.</p> <p>23 Do you recognize 801 and 801B?</p> <p>24 A. Yes.</p> <p>25 Q. Dr. McGill, where in your</p>	<p style="text-align: right;">Page 44</p> <p>1 experimentally.</p> <p>2 Once you've tested them, if 3 necessary, you return to your hypothesis and 4 make revisions, and then new predictions and 5 new testing. Once you get to a point where 6 further testing is no longer necessary, you 7 would publish that data, the information that 8 you have, and then hopefully others will 9 replicate it.</p> <p>10 And so in a case like this, I 11 think the observation or the suggestion has 12 been made, and so based on that, there's a 13 hypothesis that I've been asked to address, 14 which -- which is described in my report; 15 does acetaminophen -- is acetaminophen 16 converted to NAPQI or is there NAPQI present 17 at all in the brain after maternal ingestion 18 of therapeutic doses of acetaminophen -- 19 excuse me -- is there NAPQI in the fetal 20 brain after maternal ingestion of therapeutic 21 doses of acetaminophen.</p> <p>22 So the prediction -- if that's 23 our hypothesis and our -- what's called 24 your -- so you would state your hypothesis as 25 a falsifiable statement. So your hypothesis</p>
<p style="text-align: right;">Page 43</p> <p>1 report do you identify and describe the 2 methodology that you employed to reach the 3 opinions you offer concerning 4 pharmacokinetics and acetaminophen?</p> <p>5 A. I didn't describe the 6 methodology in detail within the report. I 7 think it's evident from the structure of the 8 report. I'd be happy to share my methodology 9 with you, if you'd like.</p> <p>10 Q. Yeah, I'd like you to describe 11 your methodology.</p> <p>12 A. Sure.</p> <p>13 So I applied the same standard 14 that I apply in my everyday academic career 15 and my scientific work, and that is following 16 the scientific method.</p> <p>17 So the scientific method, as 18 you may be aware, progresses through a number 19 of steps. There's observation. So you 20 observe a phenomenon, an effect of some kind. 21 Based on that observation, you formulate a 22 hypothesis.</p> <p>23 Once you have a hypothesis, you 24 make predictions based on your hypothesis, 25 and then you test those predictions</p>	<p style="text-align: right;">Page 45</p> <p>1 might be that acetaminophen is converted to 2 NAPQI in the brain.</p> <p>3 So then the prediction that you 4 would make -- and let me clarify. The null 5 hypothesis, which is also an important 6 hypothesis, is that that doesn't happen.</p> <p>7 So the prediction that you 8 would make based on the hypothesis is, for 9 example, one prediction you could make, that 10 I personally made, is that if there is NAPQI 11 present in the brain after acetaminophen 12 exposure, then you would see 13 acetaminophen-protein adducts in the brain.</p> <p>14 And so I'm not doing the work 15 myself here, right, so as opposed to myself 16 testing that prediction, I look in the 17 literature to see if anyone else has tested 18 it. In this case it has been tested and it's 19 found that there's no NAPQI present in the 20 brain, even after massive overdoses of 21 acetaminophen, but we can, of course, get 22 into that later.</p> <p>23 And so I see those -- that's an 24 example of how I would approach it. And then 25 also look for people who have replicated</p>

<p style="text-align: right;">Page 46</p> <p>1 those data.</p> <p>2 Q. You started out your answer</p> <p>3 long ago by saying that part of the</p> <p>4 scientific method includes testing and</p> <p>5 further testing, did you not?</p> <p>6 MR. COHEN: Object to the form.</p> <p>7 A. The method -- again, the</p> <p>8 progression is observation, hypothesis,</p> <p>9 prediction, testing, revision, if necessary,</p> <p>10 and then replication.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. What testing did you perform as</p> <p>13 part of your scientific method?</p> <p>14 A. Yeah, as I stated in my answer,</p> <p>15 I didn't do the testing myself in this case</p> <p>16 because I'm -- I was asked to review the</p> <p>17 literature, right? And so instead of doing</p> <p>18 it myself, I look in the literature to see if</p> <p>19 anyone else has made the same predictions or</p> <p>20 tested the same predictions.</p> <p>21 Q. Fair to say that tests</p> <p>22 concerning developmental neurotoxicology are</p> <p>23 particularly relevant in this case?</p> <p>24 A. Well, the questions that I've</p> <p>25 been asked to address are about does</p>	<p style="text-align: right;">Page 48</p> <p>1 experts that you reviewed?</p> <p>2 A. Correct.</p> <p>3 Q. And --</p> <p>4 A. So in that paragraph, I state</p> <p>5 that those reports include speculation on</p> <p>6 various mechanisms by which maternal use of</p> <p>7 acetaminophen might result in ASD or ADHD in</p> <p>8 offspring.</p> <p>9 The plaintiffs' experts</p> <p>10 proposed mechanisms of acetaminophen injury</p> <p>11 to the embryonic/fetal brain -- for the</p> <p>12 record, I'm quoting from my report -- that</p> <p>13 include a formation of</p> <p>14 N-acetyl-p-benzoquinone imine, or NAPQI,</p> <p>15 however you prefer to say it, the potentially</p> <p>16 hepatotoxic metabolite in the brain -- the</p> <p>17 hepatotoxic metabolite, the potential</p> <p>18 presence of that in the brain, I should say,</p> <p>19 oxidative stress in the brain and the</p> <p>20 production of AM404.</p> <p>21 I go on to state that -- state</p> <p>22 my conclusions, which is there's no</p> <p>23 scientific evidence of NAPQI formation in the</p> <p>24 human embryonic or fetal brain sufficient to</p> <p>25 cause injury following maternal ingestion of</p>
<p style="text-align: right;">Page 47</p> <p>1 acetaminophen, number one, is it converted to</p> <p>2 NAPQI in the brain or is there NAPQI present</p> <p>3 in the brain, particularly in the fetus after</p> <p>4 maternal ingestion of therapeutic doses, and</p> <p>5 then also is there oxidative stress in the</p> <p>6 brain and is -- is, basically, AM404 a</p> <p>7 plausible metabolite that could mediate</p> <p>8 biological effects after therapeutic doses of</p> <p>9 acetaminophen.</p> <p>10 Q. Where is your hypothesis listed</p> <p>11 in your report?</p> <p>12 A. Well, again, I think it's</p> <p>13 evident from the structure of the report,</p> <p>14 so --</p> <p>15 Q. It's not evident to me, so can</p> <p>16 you point me to the page and paragraph where</p> <p>17 it's listed?</p> <p>18 MR. COHEN: Object to the form.</p> <p>19 I don't think he was finished.</p> <p>20 A. So particularly if you look at</p> <p>21 paragraph 4. I'll just wait a moment.</p> <p>22 (Pause.)</p> <p>23 BY MR. JANUSH:</p> <p>24 Q. Is that the paragraph that</p> <p>25 begins with the reports of plaintiffs'</p>	<p style="text-align: right;">Page 49</p> <p>1 therapeutic doses of acetaminophen.</p> <p>2 There's no scientific evidence</p> <p>3 of oxidative stress in the human embryonic or</p> <p>4 fetal brain following maternal ingestion of</p> <p>5 therapeutic doses of acetaminophen.</p> <p>6 And there's no scientific</p> <p>7 evidence that AM404 exists in the human</p> <p>8 embryonic or fetal brain or has adverse</p> <p>9 biological effects following maternal</p> <p>10 ingestion of therapeutic doses of</p> <p>11 acetaminophen.</p> <p>12 So I've laid out what</p> <p>13 mechanisms the plaintiffs propose that I was</p> <p>14 asked to address. And that is the</p> <p>15 hypothesis. That -- those are the</p> <p>16 hypotheses.</p> <p>17 Q. And what's your null</p> <p>18 hypothesis?</p> <p>19 A. Right. So for each one, the</p> <p>20 null hypothesis would be that there isn't</p> <p>21 NAPQI in the brain; there isn't oxidative</p> <p>22 stress in the brain; and that you don't</p> <p>23 produce enough AM404 in the brain to have</p> <p>24 adverse effects on -- enough of those to have</p> <p>25 adverse effects in question, or at all in</p>

<p style="text-align: right;">Page 50</p> <p>1 some cases.</p> <p>2 Q. In order to arrive at opinions</p> <p>3 you're offering in your report, one of the</p> <p>4 things you did was review the report</p> <p>5 submitted by plaintiffs' experts, right?</p> <p>6 A. I reviewed their reports, yes.</p> <p>7 Q. And then you reviewed certain</p> <p>8 studies, right?</p> <p>9 A. Yes.</p> <p>10 Q. Anything else?</p> <p>11 A. So in my review of the studies,</p> <p>12 the way that I approach that typically is I</p> <p>13 do a literature search using relevant search</p> <p>14 terms, and then when I identify literature</p> <p>15 that appears to be relevant from those</p> <p>16 searches, I examine those papers.</p> <p>17 If they cite literature in</p> <p>18 those papers that may also be relevant, I</p> <p>19 review that information, those papers, and</p> <p>20 then -- so I obtain additional literature in</p> <p>21 that way. So through literature searches,</p> <p>22 through other literature that's cited in the</p> <p>23 papers that I get from those searches.</p> <p>24 I also have done my own</p> <p>25 obviously extensive research in the area of</p>	<p style="text-align: right;">Page 52</p> <p>1 or acetaminophen -- or brain and CYP2E1 and</p> <p>2 fetal. Those are just examples.</p> <p>3 Once I've done that search, my</p> <p>4 approach then is to go back to the earliest</p> <p>5 study, so sort the studies by date, go back</p> <p>6 to the very first one and then work my way</p> <p>7 forward in time. Because understanding where</p> <p>8 we start helps me to understand where we are</p> <p>9 now, to how we get there.</p> <p>10 As I go through those studies,</p> <p>11 I use what's a typical approach and what we</p> <p>12 could call a systematic review, which is a</p> <p>13 very common type of review that's often</p> <p>14 published, and where I initially review the</p> <p>15 title and abstract for relevance.</p> <p>16 You know, so an example that I</p> <p>17 could give for nonrelevance might be there's</p> <p>18 a paper where they looked at, you know, the</p> <p>19 effect of a natural product on acetaminophen</p> <p>20 toxicity in the liver and then the effect of</p> <p>21 a natural product on something else in the</p> <p>22 brain. So the search terms that I use could</p> <p>23 yield something like that.</p> <p>24 Well, that's not addressing the</p> <p>25 topic here, right? That's about some natural</p>
<p style="text-align: right;">Page 51</p> <p>1 acetaminophen metabolism and toxicity, and</p> <p>2 then in addition to that, defense counsel has</p> <p>3 provided a little bit of literature.</p> <p>4 Q. Could you describe the criteria</p> <p>5 you employed to set -- to select the</p> <p>6 appropriate studies for your analysis? I</p> <p>7 understand that you've addressed that you</p> <p>8 used search terms, but I want the criteria,</p> <p>9 and then thereafter, I'm going to follow up</p> <p>10 with asking you about your specific search</p> <p>11 terms.</p> <p>12 MR. COHEN: Object to form.</p> <p>13 Go ahead.</p> <p>14 A. So I used the same approach</p> <p>15 that I use anytime I'm evaluating the</p> <p>16 literature in my regular scientific work, so</p> <p>17 applying the same standards.</p> <p>18 That approach is typically</p> <p>19 search at least one database, such as, for</p> <p>20 example, Medline or PubMed. They're</p> <p>21 essentially the same thing. And then I would</p> <p>22 perform that search using Boolean search</p> <p>23 terms. So for -- just as an example, since</p> <p>24 you alluded to search terms, one example I</p> <p>25 could give would be acetaminophen and brain</p>	<p style="text-align: right;">Page 53</p> <p>1 product in the brain and then also in the</p> <p>2 liver, so I would filter that out. I would</p> <p>3 consider that irrelevant.</p> <p>4 So I would go through each</p> <p>5 paper step by step like that. Once I've</p> <p>6 collected all the papers that are relevant to</p> <p>7 the topic, then I go through and review them.</p> <p>8 BY MR. JANUSH:</p> <p>9 Q. We don't have your search</p> <p>10 terms, right? You didn't provide that to us</p> <p>11 in your report; is that right?</p> <p>12 A. That's correct.</p> <p>13 Q. So we can't reproduce your</p> <p>14 analysis, can we?</p> <p>15 MR. COHEN: Object to the form.</p> <p>16 A. Again, the approach that I used</p> <p>17 is very standard. Anyone has -- you know,</p> <p>18 PubMed is a publicly accessible database.</p> <p>19 Anyone can go in there and perform very</p> <p>20 similar searches, and it's a very -- in my</p> <p>21 field it's a very, very standard approach to</p> <p>22 a systematic review of the literature. So</p> <p>23 it's what I would expect most people to do.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. But while PubMed is widely</p>

<p style="text-align: right;">Page 54</p> <p>1 available and I can go online and access it</p> <p>2 right now, would you agree that I don't have</p> <p>3 your search terms publicly available to</p> <p>4 reproduce your methodology as to how you</p> <p>5 selected your literature?</p> <p>6 MR. COHEN: Object to form.</p> <p>7 A. Well, I just provided a couple</p> <p>8 of examples of search terms. I did not list</p> <p>9 them in this report.</p> <p>10 BY MR. JANUSH:</p> <p>11 Q. Right. You would agree with</p> <p>12 me -- would you agree with me that the couple</p> <p>13 of examples you provided are -- are nowhere</p> <p>14 near the total search terms that you would</p> <p>15 have used, or are they?</p> <p>16 Do they represent the search</p> <p>17 terms that you utilized and nothing more in</p> <p>18 arriving at your -- the literature you</p> <p>19 reviewed?</p> <p>20 A. Well, so again, just to be</p> <p>21 clear, the literature that I reviewed comes</p> <p>22 not just from searches. It comes from</p> <p>23 studies referenced as -- referenced by the</p> <p>24 studies that came up in my -- the relevant</p> <p>25 studies that come up in my search terms. It</p>	<p style="text-align: right;">Page 56</p> <p>1 over in your searches and in your review of</p> <p>2 the literature and that sort of thing.</p> <p>3 But again, it's a -- that's a</p> <p>4 common approach and it's common because it's</p> <p>5 exhaustive.</p> <p>6 Q. Are you aware that Dr. Powell</p> <p>7 and Johnson & Johnson Consumer Inc. used</p> <p>8 different search terms in their review of the</p> <p>9 preclinical literature?</p> <p>10 MR. COHEN: Object to form.</p> <p>11 A. Well, Dr. Powell and I are</p> <p>12 addressing different issues. Oh, I'm sorry,</p> <p>13 you mean between Johnson & Johnson and</p> <p>14 Dr. Powell there are differences?</p> <p>15 I -- I have no information</p> <p>16 about Johnson & Johnson's searches.</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. Do you know -- let me ask --</p> <p>19 sorry, apologize, I'm going to ask a</p> <p>20 different question.</p> <p>21 Are you aware of what search</p> <p>22 terms Dr. Powell used in his review of</p> <p>23 preclinical literature?</p> <p>24 A. I reviewed Dr. Powell's report,</p> <p>25 but I don't remember exactly what he said</p>
<p style="text-align: right;">Page 55</p> <p>1 comes from my own research, and it comes from</p> <p>2 some documents provided by the defense</p> <p>3 counsel.</p> <p>4 Now, in terms of answering your</p> <p>5 question more directly, I don't recall the</p> <p>6 number of search terms that I used. And</p> <p>7 again, I -- as I've said, I didn't provide</p> <p>8 them directly in my report.</p> <p>9 Q. What did you do to satisfy</p> <p>10 yourself that your search was exhaustive?</p> <p>11 A. So again, that systematic</p> <p>12 approach is a common practice in the field.</p> <p>13 It's kind of the standard approach in my</p> <p>14 field to a review of the literature. It's</p> <p>15 done that way because it's an exhaustive</p> <p>16 approach.</p> <p>17 Again, we're going back to the</p> <p>18 very beginning and moving forward. And</p> <p>19 again, I'm not just relying on the results</p> <p>20 that I get from that search. I look at</p> <p>21 references that are provided in those papers,</p> <p>22 so you get kind of a network of literature.</p> <p>23 And one way you can tell you've</p> <p>24 pretty much seen what's out there is when you</p> <p>25 start seeing the same references over and</p>	<p style="text-align: right;">Page 57</p> <p>1 about his methodology.</p> <p>2 Q. So two different scientists</p> <p>3 with two different search methodologies and</p> <p>4 two different sets of search terms might come</p> <p>5 up with different results, right?</p> <p>6 MR. COHEN: Object to form.</p> <p>7 A. Well, that's why you employ</p> <p>8 multiple different search terms to avoid --</p> <p>9 so my expectation would be if I did only one</p> <p>10 search and the other individual did only one</p> <p>11 search with different search terms, there</p> <p>12 would be -- assuming it's on the same topic,</p> <p>13 right -- then there would be considerable</p> <p>14 overlap, but there might be a few different</p> <p>15 studies. But that's why you use multiple</p> <p>16 search terms.</p> <p>17 So if I used multiple search</p> <p>18 terms and the other person uses multiple</p> <p>19 search terms, then I would expect us to</p> <p>20 arrive at nearly identical results.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. Is transparency important in</p> <p>23 science?</p> <p>24 A. That's, again, quite a broad</p> <p>25 question. Transparency in terms of what</p>

<p style="text-align: right;">Page 58</p> <p>1 you've done and the data you've collected?</p> <p>2 Q. Yes.</p> <p>3 A. Yes.</p> <p>4 Q. What does transparency mean to</p> <p>5 you in fulfilling your role as an expert in</p> <p>6 this case?</p> <p>7 MR. COHEN: Object to the form.</p> <p>8 A. Well, I mean, I've -- in</p> <p>9 terms -- if we're still just talking about,</p> <p>10 right, the scientific content, being</p> <p>11 transparent is sharing the results of my</p> <p>12 review of the literature and doing so</p> <p>13 accurately.</p> <p>14 BY MR. JANUSH:</p> <p>15 Q. If I asked you right now, could</p> <p>16 you provide me, after this deposition ended,</p> <p>17 with a list of your search terms and the way</p> <p>18 you approached your searches to obtain the</p> <p>19 literature you utilized in your report, could</p> <p>20 you do it?</p> <p>21 MR. COHEN: Object to the form.</p> <p>22 A. I could provide you with --</p> <p>23 excuse me -- multiple search terms that I</p> <p>24 believe would yield the same studies.</p> <p>25 ///</p>	<p style="text-align: right;">Page 60</p> <p>1 MR. COHEN: Object to the form.</p> <p>2 We'll take it under advisement.</p> <p>3 A. I -- I don't think I can</p> <p>4 agree -- I would agree to anything without</p> <p>5 discussing it -- without thinking it over and</p> <p>6 discussing it.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. Is it good or bad for a</p> <p>9 scientist to cherry-pick literature?</p> <p>10 MR. COHEN: Object to the form.</p> <p>11 A. Well, personally, I try to</p> <p>12 avoid it. I think at least one of your</p> <p>13 expert witnesses has done that, and --</p> <p>14 MR. JANUSH: Move to strike,</p> <p>15 nonresponsive.</p> <p>16 BY MR. JANUSH:</p> <p>17 Q. I just asked you if it's a good</p> <p>18 thing or a bad thing to cherry-pick</p> <p>19 literature when serving as an expert.</p> <p>20 MR. COHEN: Object to the form.</p> <p>21 A. Sorry, when serving as an</p> <p>22 expert specifically? Yeah, I -- I would not</p> <p>23 cherry-pick literature. Again, I think at</p> <p>24 least one of your plaintiff experts has done</p> <p>25 so.</p>
<p style="text-align: right;">Page 59</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. How about the actual search</p> <p>3 terms that you utilized, could you provide me</p> <p>4 with that?</p> <p>5 MR. COHEN: Object to the form.</p> <p>6 A. I...</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. In other words, did you retain</p> <p>9 your search terms?</p> <p>10 A. I'm trying to consider the</p> <p>11 question and answer it accurately.</p> <p>12 Again, I could easily provide</p> <p>13 you a list of search terms that would yield</p> <p>14 the same results.</p> <p>15 Q. You could provide me with a</p> <p>16 list of search terms that would yield the</p> <p>17 same results as all of the literature that</p> <p>18 you have addressed in your report; is that</p> <p>19 your testimony today?</p> <p>20 MR. COHEN: Object to the form.</p> <p>21 A. At least the majority of the</p> <p>22 results, yeah.</p> <p>23 BY MR. JANUSH:</p> <p>24 Q. Would you agree to do that</p> <p>25 after this deposition ends?</p>	<p style="text-align: right;">Page 61</p> <p>1 MR. JANUSH: Move to strike the</p> <p>2 latter part of the gratuitous answer</p> <p>3 beginning with "at least" and ending</p> <p>4 with "done so."</p> <p>5 BY MR. JANUSH:</p> <p>6 Q. Were there any limitations or</p> <p>7 challenges you encountered while applying</p> <p>8 your claimed scientific method to your</p> <p>9 assignment?</p> <p>10 MR. COHEN: Object to the form.</p> <p>11 A. Sorry, can you ask the question</p> <p>12 again?</p> <p>13 BY MR. JANUSH:</p> <p>14 Q. Were there any limitations or</p> <p>15 challenges that you encountered when applying</p> <p>16 your claimed scientific method to your</p> <p>17 assignment in this case?</p> <p>18 MR. COHEN: Same objection.</p> <p>19 A. No, not off the top of my head.</p> <p>20 Again, my approach is standard in the field.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. As part of your literature</p> <p>23 review, did you look at and consider the</p> <p>24 studies addressed before your expert report</p> <p>25 was due by plaintiffs' experts?</p>

<p style="text-align: right;">Page 62</p> <p>1 A. Can you ask the question -- I</p> <p>2 want to make sure I understand --</p> <p>3 Q. You understand that before your</p> <p>4 expert report was due, plaintiffs had to</p> <p>5 serve their expert reports, right?</p> <p>6 A. Yes.</p> <p>7 Q. And you -- you had an</p> <p>8 opportunity to receive those expert reports,</p> <p>9 right?</p> <p>10 A. Yes.</p> <p>11 Q. And you had an opportunity to</p> <p>12 review those reports, right?</p> <p>13 A. Yes.</p> <p>14 Q. And you did review them, right?</p> <p>15 A. Yes, my report contains some</p> <p>16 responses to those.</p> <p>17 Q. I understand that.</p> <p>18 Did you -- how did you go about</p> <p>19 addressing which of the articles or pieces of</p> <p>20 literature you would include in your</p> <p>21 materials reviewed list?</p> <p>22 A. Well, I mean, we included</p> <p>23 everything that I -- I referenced, every</p> <p>24 study that I went over in my report as well</p> <p>25 as other relevant studies that we -- that I</p>	<p style="text-align: right;">Page 64</p> <p>1 in -- let's say they're testing a natural</p> <p>2 product, a dietary supplement, botanical</p> <p>3 extract, something like that. They want to</p> <p>4 know if it affects the liver, and then they</p> <p>5 may also have an additional question about,</p> <p>6 you know, does it have any impact on the</p> <p>7 brain.</p> <p>8 So they do two different</p> <p>9 studies, but they are in the same paper, but</p> <p>10 the study relative to the brain has nothing</p> <p>11 to do with acetaminophen. So that would</p> <p>12 obviously not be a relevant paper and I would</p> <p>13 exclude that.</p> <p>14 Q. Fair to say that</p> <p>15 "acetaminophen" was a fundamental term in</p> <p>16 your searches?</p> <p>17 A. For parts of -- for some of my</p> <p>18 searches. There are others where I was just</p> <p>19 looking at P450 levels in the brain in</p> <p>20 comparison to the liver, and so those</p> <p>21 studies -- those, sorry, search terms would</p> <p>22 not have included "acetaminophen."</p> <p>23 And I'm trying to recall.</p> <p>24 There may have been additional cases where I</p> <p>25 would not have included the term</p>
<p style="text-align: right;">Page 63</p> <p>1 found in the process of doing my literature</p> <p>2 searches and reviewing the report as well as</p> <p>3 any relevant literature that I identified</p> <p>4 when reviewing the plaintiffs' experts'</p> <p>5 reports.</p> <p>6 I mean, essentially, with</p> <p>7 regard to the reference list, it just</p> <p>8 includes basically everything that we -- that</p> <p>9 I looked at.</p> <p>10 Q. Your reference list includes</p> <p>11 everything you looked at in this case. Fair</p> <p>12 to say?</p> <p>13 A. Except those things that I</p> <p>14 ruled out as irrelevant, as I described when</p> <p>15 discussing my methodology.</p> <p>16 Q. What types of literature did</p> <p>17 you rule out as irrelevant?</p> <p>18 A. Yeah, I described that in my</p> <p>19 previous response. So an example would be,</p> <p>20 you know, let's say again, search term is</p> <p>21 acetaminophen and brain, right? That's a</p> <p>22 Boolean search term, so return anything that</p> <p>23 mentions both acetaminophen and the brain.</p> <p>24 So -- but there might be a</p> <p>25 study where, for example, they're interested</p>	<p style="text-align: right;">Page 65</p> <p>1 "acetaminophen," but yeah.</p> <p>2 Q. Did you include search terms</p> <p>3 about gestation?</p> <p>4 A. I don't recall for sure. I</p> <p>5 included search terms about -- certainly</p> <p>6 about fetal, embryonic, neurodevelopment. I</p> <p>7 don't recall if I specifically used the term</p> <p>8 "gestation." I may have.</p> <p>9 Q. Did you use the term</p> <p>10 "neurodevelopment"?</p> <p>11 A. Yes.</p> <p>12 Q. How about "lactation"?</p> <p>13 A. This case is not -- again, I</p> <p>14 can't say -- I can't recall for certain.</p> <p>15 Since this case is not addressing exposure</p> <p>16 through the mother's milk, I may not have</p> <p>17 included that term.</p> <p>18 Q. You understand that postnatal</p> <p>19 day 10 is a neonatal period when we're</p> <p>20 speaking about mice being studied, right?</p> <p>21 A. I am not an expert in how</p> <p>22 animal-mouse neurodevelopment translates to</p> <p>23 human neurodevelopment. I understand that</p> <p>24 there are studies in which that claim is</p> <p>25 made, but I can't assess the claim.</p>

<p>Page 66</p> <p>1 Q. Did you purposefully avoid</p> <p>2 mouse-rodent neurodevelopmental studies</p> <p>3 concerning acetaminophen exposure because you</p> <p>4 are, quote, not an expert on that topic?</p> <p>5 MR. COHEN: Object to form.</p> <p>6 A. No, I did not purposefully</p> <p>7 avoid any of those -- any such studies.</p> <p>8 BY MR. JANUSH:</p> <p>9 Q. Do you agree that within your</p> <p>10 report you didn't grade the animal literature</p> <p>11 studying APAP for neurodevelopmental</p> <p>12 disorders?</p> <p>13 A. In my area of research, that is</p> <p>14 not common practice.</p> <p>15 Q. So you didn't do it, right?</p> <p>16 A. I assessed the strength of the</p> <p>17 data based on common considerations and</p> <p>18 science. For example, necessary but</p> <p>19 sufficient, necessary and sufficient,</p> <p>20 necessary and not sufficient or is -- you --</p> <p>21 as a scientist, of course, you always wait as</p> <p>22 one experiment is better to address this</p> <p>23 question than another.</p> <p>24 So, for example, to me, the</p> <p>25 ultimate experiment in this case that has</p>	<p>Page 68</p> <p>1 brain. So the exosome question essentially</p> <p>2 becomes irrelevant.</p> <p>3 I'm happy to discuss it if</p> <p>4 you'd like, but that's an example that I just</p> <p>5 wanted to give of how you would weight the</p> <p>6 data, right, looking at an actual final</p> <p>7 endpoint rather than some kind of</p> <p>8 intermediary speculative step.</p> <p>9 BY MR. JANUSH:</p> <p>10 Q. What was my question?</p> <p>11 A. Your question was</p> <p>12 essentially -- I don't recall the exact --</p> <p>13 MR. COHEN: Object. Object.</p> <p>14 Sorry.</p> <p>15 A. I don't recall the exact</p> <p>16 wording of your question. I think --</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. I'm just asking for a yes or</p> <p>19 no: Did you grade animal literature testing</p> <p>20 for acetaminophen exposure, yes or no?</p> <p>21 MR. COHEN: Object to the form.</p> <p>22 A. I don't believe it can be</p> <p>23 answered with a simple yes or no. All</p> <p>24 scientists, of course, always sort of weigh,</p> <p>25 evaluate the strength of different pieces of</p>
<p>Page 67</p> <p>1 been done is these studies where they give</p> <p>2 mice large doses of acetaminophen and look</p> <p>3 for surrogates of NAPQI formation, such as --</p> <p>4 or NAPQI presence, such as</p> <p>5 acetaminophen-protein adducts, and they find</p> <p>6 nothing. So to me, I mean, that's an</p> <p>7 outstanding piece of data.</p> <p>8 MR. JANUSH: Move to strike,</p> <p>9 nonresponsive.</p> <p>10 A. As opposed to, for example --</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. What do you think my</p> <p>13 question --</p> <p>14 MR. COHEN: No, no, no.</p> <p>15 MR. JANUSH: I'm going to stop</p> <p>16 you.</p> <p>17 MR. COHEN: No, no. No, no,</p> <p>18 no. We're not doing this. He gets to</p> <p>19 finish. You get to ask the next</p> <p>20 question. Go ahead and finish.</p> <p>21 A. As opposed to, for example,</p> <p>22 asking a question is there CYP2E1 in exosomes</p> <p>23 based on some speculation that that might</p> <p>24 contribute to NAPQI formation in the brain;</p> <p>25 well, the fact is, there's no NAPQI in the</p>	<p>Page 69</p> <p>1 evidence against each other.</p> <p>2 BY MR. JANUSH:</p> <p>3 Q. Within your report, did you</p> <p>4 grade the animal-rodent literature testing</p> <p>5 for acetaminophen for neurodevelopmental</p> <p>6 disorders? Yes or no?</p> <p>7 MR. COHEN: Object to the form</p> <p>8 of the question.</p> <p>9 A. I was not asked to address</p> <p>10 neurodevelopmental disorders or</p> <p>11 neurodevelopmental endpoints.</p> <p>12 BY MR. JANUSH:</p> <p>13 Q. I'm going to make you a deal.</p> <p>14 I'm going to try and ask really crisp, clear</p> <p>15 questions; and if I get really crisp, clear</p> <p>16 answers, your day is going to be a lot</p> <p>17 shorter, okay?</p> <p>18 MR. COHEN: Object to the</p> <p>19 colloquy. Just ask questions, please.</p> <p>20 MR. JANUSH: Oh, I am.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. Can you point me to an area</p> <p>23 within your report where you weighed the</p> <p>24 animal literature studying APAP for</p> <p>25 neurodevelopmental disorders?</p>

<p style="text-align: right;">Page 70</p> <p>1 MR. COHEN: Object to the form.</p> <p>2 A. As I've stated, all scientists</p> <p>3 are always weighing different pieces of</p> <p>4 literature, different pieces of data against</p> <p>5 each other.</p> <p>6 BY MR. JANUSH:</p> <p>7 Q. I'm not asking about all</p> <p>8 scientists. I'm asking about your report.</p> <p>9 You understand you have your</p> <p>10 report in front of you, right? Is that --</p> <p>11 can you look at it?</p> <p>12 A. This is my report.</p> <p>13 Q. Okay. Can you peel through it</p> <p>14 and show me where you graded the</p> <p>15 animal-rodent literature? It's a yes or no.</p> <p>16 You either can or you can't.</p> <p>17 MR. COHEN: Object to the form.</p> <p>18 Go ahead.</p> <p>19 A. Again, I don't think that it's</p> <p>20 a yes -- it can be answered quite so simply.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. Well, just point me to the</p> <p>23 page.</p> <p>24 A. Again, as I state, throughout</p> <p>25 my review of the literature, I weighed</p>	<p style="text-align: right;">Page 72</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. You can't, right?</p> <p>3 A. Throughout preparation of the</p> <p>4 document, I was always evaluating strengths</p> <p>5 and weaknesses of different studies and</p> <p>6 different pieces of data, as is common</p> <p>7 practice for a scientist.</p> <p>8 Q. Including -- including the</p> <p>9 available animal-rodent literature?</p> <p>10 A. The relevant available</p> <p>11 animal-rodent literature. Again, I was not</p> <p>12 asked to address neurodevelopmental outcomes.</p> <p>13 Q. You were not asked to address</p> <p>14 neurodevelopmental outcomes?</p> <p>15 MR. COHEN: Is that the</p> <p>16 question?</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. Is that your testimony?</p> <p>19 MR. COHEN: Sorry. Go ahead.</p> <p>20 A. Yes. With the caveat that the</p> <p>21 questions I was asked to address, the</p> <p>22 plaintiffs' experts have proposed that they</p> <p>23 are relevant to those types of outcomes.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. And so you didn't seek to</p>
<p style="text-align: right;">Page 71</p> <p>1 different pieces of evidence against each</p> <p>2 other, as is the common practice for a</p> <p>3 scientist.</p> <p>4 Q. Do you grade studies when</p> <p>5 authoring -- when authoring review articles?</p> <p>6 A. Again, we weigh -- weigh</p> <p>7 different pieces of evidence, different</p> <p>8 pieces of literature against each other.</p> <p>9 Q. But in your report, right now,</p> <p>10 can you point me to any area where you graded</p> <p>11 animal-rodent literature?</p> <p>12 A. Yeah, again, my answer remains</p> <p>13 the same, that you -- I always evaluate</p> <p>14 strengths and weaknesses. That's part of a</p> <p>15 critical evaluation of the literature.</p> <p>16 Q. But where is it? That's what</p> <p>17 I'm asking. Can you show it to me?</p> <p>18 A. The -- what I've written in my</p> <p>19 report is the result of the critical</p> <p>20 evaluation of the literature.</p> <p>21 Q. I'm not asking about what you</p> <p>22 wrote. Can you show me where you graded the</p> <p>23 rodent literature?</p> <p>24 MR. COHEN: Object to the form.</p> <p>25 ///</p>	<p style="text-align: right;">Page 73</p> <p>1 counter the plaintiffs' claims that they are</p> <p>2 relevant to those types of outcomes because</p> <p>3 you didn't -- you're not a neurodevelopmental</p> <p>4 expert, right?</p> <p>5 A. I do counter the plaintiffs'</p> <p>6 claims with respect to the issues that I've</p> <p>7 outlined in paragraph 4.</p> <p>8 Q. Okay. Dr. McGill, if an expert</p> <p>9 issuing an opinion on general causation</p> <p>10 selectively picks literature from the</p> <p>11 scientific landscape and presents the court</p> <p>12 with what that expert believes the relevant</p> <p>13 studies demonstrate, would that be a good</p> <p>14 thing to do or a bad thing to do in</p> <p>15 fulfilling an expert role?</p> <p>16 MR. COHEN: Object to the form.</p> <p>17 A. Well, in terms of general</p> <p>18 causation, that's not what I was asked to</p> <p>19 address, and I wouldn't consider that --</p> <p>20 causation in the sense of epidemiology and</p> <p>21 genetics and that sort of thing, what factors</p> <p>22 weigh heavily into clinical outcomes. That's</p> <p>23 not my expertise.</p> <p>24 In general, yeah, you wouldn't</p> <p>25 want to cherry-pick studies or data.</p>

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1 BY MR. JANUSH:

2 Q. Cherry-picking would be bad,

3 right?

4 MR. COHEN: Object to the form.

5 A. Yeah, which is one of the

6 issues that I have with at least one of your

7 plaintiffs.

8 MR. JANUSH: Move to strike the

9 latter part of your answer.

10 BY MR. JANUSH:

11 Q. And the reason from a

12 scientific perspective that cherry-picking

13 literature is bad is because it would be a

14 form of a result-driven analysis that

15 undermines principles of the scientific

16 method, right?

17 MR. COHEN: Object to the form.

18 A. A result-driven analysis? I

19 mean, the way I would characterize it is that

20 ignoring relevant data is -- could

21 potentially lead to inaccurate conclusions.

22 BY MR. JANUSH:

23 Q. And assessing the weight of the

24 literature as we were discussing before, it

25 was part of your methodology that you did not

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1 disclose in your report, right?

2 MR. COHEN: Object to the form.

3 A. Again, it's -- it's a standard

4 practice in my field to -- I mean, that is

5 just the fundamental part of science, that

6 when you are considering claims that are

7 based on or purportedly based on science, you

8 evaluate the strengths and weaknesses of the

9 available data.

10 BY MR. JANUSH:

11 Q. I'm not asking what you

12 evaluate as a scientist. I'm addressing your

13 report.

14 Assessing the weight of the

15 literature was part of your methodology that

16 you did not set forth in your report?

17 MR. COHEN: Object to the form.

18 BY MR. JANUSH:

19 Q. Is that right?

20 MR. COHEN: Go ahead.

21 A. Assessing strengths and

22 weaknesses of studies is an intrinsic part of

23 writing a review, any kind of review,

24 including an expert report.

25 ///

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1 BY MR. JANUSH:

2 Q. But assessing the weight of the

3 literature, the strengths and weaknesses of

4 literature, for example, the body of rodent

5 studies addressing developmental

6 neurotoxicology associated with

7 acetaminophen, you didn't evaluate the

8 strengths and weaknesses of most of those

9 studies, right?

10 MR. COHEN: Object to form.

11 A. Again, I was not asked to

12 evaluate any neurodevelopmental or behavioral

13 studies, so that's not my goal here.

14 BY MR. JANUSH:

15 Q. Even -- even when those

16 neurodevelopmental and behavioral studies

17 concerned acetaminophen; is that right?

18 MR. COHEN: Object to form.

19 A. As I've stated, I was not asked

20 to address neurodevelopmental outcomes or

21 neurodevelopmental studies.

22 BY MR. JANUSH:

23 Q. What's this case about?

24 MR. COHEN: Object to form.

25 A. The issues that I was asked to

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1 address in this case --

2 BY MR. JANUSH:

3 Q. Not what I'm asking.

4 What do you understand this

5 case is about? Let me ask it differently.

6 Do you have an understanding

7 that this case is about mothers and parents

8 claiming that pregnant women took

9 acetaminophen, such as Tylenol, during

10 pregnancy and gave birth to children with

11 neurodevelopmental disorders such as ASD,

12 autism spectrum disorder, and ADHD, who were

13 exposed to acetaminophen in utero?

14 Do you understand that?

15 A. I understand that the -- at

16 least some of the plaintiffs are claiming

17 that -- basically claiming injury due to --

18 for their children due to in utero exposure

19 to therapeutic doses of acetaminophen.

20 Q. In other words, this case is

21 about developmental in utero neurotoxicology,

22 isn't it?

23 MR. COHEN: Object to form.

24 A. This case is about the claims

25 of the plaintiffs, right, and your

<p style="text-align: right;">Page 78</p> <p>1 plaintiffs' experts proposed, as I laid out</p> <p>2 in paragraph 4, a few mechanisms by which</p> <p>3 that might occur. And that's what I was</p> <p>4 asked to address, so that's what I'm</p> <p>5 addressing.</p> <p>6 BY MR. JANUSH:</p> <p>7 Q. Okay. I am going to give you a</p> <p>8 demonstrative that I'll have our technician</p> <p>9 pull up on the screen as well. It's marked</p> <p>10 as Plaintiffs' Exhibit 802.</p> <p>11 (Whereupon, Deposition</p> <p>12 Exhibit P802, Demonstrative Chart,</p> <p>13 APAP-Rodent DNT Studies in McGill</p> <p>14 Report, was marked for</p> <p>15 identification.)</p> <p>16 BY MR. JANUSH:</p> <p>17 Q. It's a chart -- it's a chart,</p> <p>18 Dr. McGill, of 26 animal studies that were</p> <p>19 addressed by Dr. Pearson -- you remember</p> <p>20 reading Dr. Pearson's report, right?</p> <p>21 A. Yes.</p> <p>22 Q. And these are all of the rodent</p> <p>23 literature addressed by Dr. Pearson --</p> <p>24 actually, it's 25 lines, not 26. The first</p> <p>25 lines at the top are Author, Title, Year.</p>	<p style="text-align: right;">Page 80</p> <p>1 well, let's look at Beck. You didn't mention</p> <p>2 Beck in your report, right, Spatial</p> <p>3 Glutathione and Cysteine Distribution and</p> <p>4 Chemical Modulation in the Early</p> <p>5 Organogenesis-Stage Rat Conceptus in Utero?</p> <p>6 MR. COHEN: Object to the form</p> <p>7 of the question.</p> <p>8 A. Understand when I answer these</p> <p>9 questions, I'm relying on your document.</p> <p>10 Based on this document, I didn't address it.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. So we show three rodent</p> <p>13 studies: At line item 17, the Koehn study;</p> <p>14 line item 18, the Klein study; and line item</p> <p>15 21, the Rigobello study, that you</p> <p>16 addressed -- mentioned in your report.</p> <p>17 Do you see that?</p> <p>18 A. Yes.</p> <p>19 Q. And then separately, when we</p> <p>20 look at analyzed in your report, we show</p> <p>21 those same line items, those same three</p> <p>22 studies. And then there's a host of studies</p> <p>23 on your considered list that aren't even</p> <p>24 present on your considered list, the Beck</p> <p>25 study, the --</p>
<p style="text-align: right;">Page 79</p> <p>1 Column E is Mentioned in McGill Report.</p> <p>2 Column F is Analyzed in McGill Report.</p> <p>3 Column G is on McGill Materials Considered</p> <p>4 List. And column H is whether it's mice or</p> <p>5 rats.</p> <p>6 Do you see that?</p> <p>7 MR. COHEN: Just before you</p> <p>8 continue, Counsel, is this part of</p> <p>9 Dr. Pearson's report?</p> <p>10 MR. JANUSH: No. I said this</p> <p>11 is a demonstrative that I'm addressing</p> <p>12 for demonstrative purposes.</p> <p>13 MR. COHEN: Okay. Well, just</p> <p>14 standing objection to the use of</p> <p>15 demonstratives like this that have</p> <p>16 been created by lawyers for the</p> <p>17 purpose of this deposition. We're</p> <p>18 going to object to this. We're going</p> <p>19 to object to them being even marked as</p> <p>20 exhibits and being put on the record</p> <p>21 as exhibits. This is -- we don't</p> <p>22 think it's proper, but you can go</p> <p>23 ahead and ask questions.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. Dr. McGill, we show that --</p>	<p style="text-align: right;">Page 81</p> <p>1 And by the way, you don't have</p> <p>2 to trust me. You have your materials</p> <p>3 considered list in front of you appended to</p> <p>4 your report. You can feel free to</p> <p>5 cross-check me. You can open it up and</p> <p>6 cross-check me. You can tell me if I'm</p> <p>7 wrong, so feel free to do that.</p> <p>8 But we show that you didn't</p> <p>9 address the Beck study.</p> <p>10 You didn't address the</p> <p>11 Blecharz-Klin study, Effect of Prenatal and</p> <p>12 Early Life Paracetamol Exposure on the Level</p> <p>13 of Neurotransmitters in Rats, with a focus on</p> <p>14 the spinal cord.</p> <p>15 You didn't address the</p> <p>16 Blecharz-Klin study Developmental Exposure to</p> <p>17 Paracetamol Causes Biochemical Alterations in</p> <p>18 Medulla Oblongata.</p> <p>19 You didn't address</p> <p>20 Blecharz-Klin Cerebral [sic] Level of</p> <p>21 Neurotransmitters in Rats Exposed to</p> <p>22 Paracetamol During Development.</p> <p>23 You didn't -- and I say</p> <p>24 address. "Consider" is the appropriate word,</p> <p>25 so forgive me -- Philippot at line 19,</p>

<p style="text-align: right;">Page 82</p> <p>1 Evaluation of the Dentate Gyrus in Adult Mice</p> <p>2 Exposed to Acetaminophen on Postnatal Day 10.</p> <p>3 Suda, Therapeutic Doses of</p> <p>4 Acetaminophen with Co-administration of</p> <p>5 Cysteine and Mannitol During Early</p> <p>6 Development Result in Long-Term Behavioral</p> <p>7 Changes in Laboratory Rats.</p> <p>8 Didn't address 22, Philippot,</p> <p>9 Paracetamol (Acetaminophen) and Its Effect on</p> <p>10 the Developing Mouse Brain.</p> <p>11 Didn't address -- or consider,</p> <p>12 sorry -- as to everything when I'm saying</p> <p>13 address here, we're on the materials</p> <p>14 considered list.</p> <p>15 You didn't consider Herrington,</p> <p>16 Elevated Ghrelin Alters the Behavioral</p> <p>17 Effects of Perinatal Acetaminophen Exposure</p> <p>18 in Rats.</p> <p>19 Didn't address Harshaw,</p> <p>20 Interleukin-1-beta-Induced Inflammation and</p> <p>21 Acetaminophen During Infancy: Distinct and</p> <p>22 Interactive Effects on Social-Emotional and</p> <p>23 Repetitive Behavior in C57BL/6J mice.</p> <p>24 Didn't address Baker,</p> <p>25 Sex-Specific Neurobehavioral and Prefrontal</p>	<p style="text-align: right;">Page 84</p> <p>1 appreciate that, right?</p> <p>2 A. Based on your evaluation of</p> <p>3 those materials.</p> <p>4 MR. COHEN: Yeah, object to the</p> <p>5 form.</p> <p>6 A. Yes.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. So why don't we not base it on</p> <p>9 my evaluation. Open your report, turn to</p> <p>10 your materials considered list. Check me.</p> <p>11 Show me where you considered Beck.</p> <p>12 A. What I'd like to point out --</p> <p>13 I'm happy to go through these --</p> <p>14 Q. I just want you to go through</p> <p>15 it. And I'm just asking you to tell me --</p> <p>16 MR. COHEN: Just answer his</p> <p>17 questions.</p> <p>18 BY MR. JANUSH:</p> <p>19 Q. My question is show me where</p> <p>20 you considered Beck.</p> <p>21 A. Beck is not on my materials</p> <p>22 considered list.</p> <p>23 Q. Show me where you considered</p> <p>24 Dean -- excuse me, not Dean. Blecharz-Klin.</p> <p>25 A. There are two. Either one</p>
<p style="text-align: right;">Page 83</p> <p>1 Cortex Gene Expression Alterations --</p> <p>2 A. Sorry, you're saying I didn't</p> <p>3 consider --</p> <p>4 Q. Didn't -- sorry --</p> <p>5 A. -- it, but if you look at</p> <p>6 Baker, it does say yes.</p> <p>7 Q. Sorry, apologize. That's where</p> <p>8 you didn't mention it in your report. So you</p> <p>9 considered Baker but didn't mention Baker in</p> <p>10 your report, right?</p> <p>11 A. I --</p> <p>12 MR. COHEN: I'm sorry, was --</p> <p>13 MR. JANUSH: In that one.</p> <p>14 MR. COHEN: This question now</p> <p>15 is about one study? Because that was</p> <p>16 a long, long question.</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. So now as to -- I actually</p> <p>19 wasn't asking a question there.</p> <p>20 MR. COHEN: Maybe the longest</p> <p>21 question in the world.</p> <p>22 BY MR. JANUSH:</p> <p>23 Q. So I'm just reading through</p> <p>24 this chart and addressing the studies you</p> <p>25 didn't list on your considered list. You</p>	<p style="text-align: right;">Page 85</p> <p>1 you're asking?</p> <p>2 Q. Both aren't on your considered</p> <p>3 list, correct? Well, there's actually more</p> <p>4 than that. There's -- Effect of Prenatal,</p> <p>5 the one starting with Effect of Prenatal,</p> <p>6 Blecharz-Klin. There are five, I think,</p> <p>7 Blecharz-Klin studies. You considered two;</p> <p>8 three, you didn't consider.</p> <p>9 You can just tell me if you</p> <p>10 count two.</p> <p>11 A. Well, what I can say is that</p> <p>12 you have two on the list that are not listed</p> <p>13 in my materials considered list.</p> <p>14 Q. Okay.</p> <p>15 A. We do have other studies by the</p> <p>16 same authors though.</p> <p>17 Q. I have three, there's another</p> <p>18 one. Cerebral Level of Neurotransmitters,</p> <p>19 that's not on your list either, right, by</p> <p>20 Blecharz-Klin.</p> <p>21 A. Can you say the name again,</p> <p>22 please.</p> <p>23 Q. Cerebral Level of</p> <p>24 Neurotransmitter in Rats Exposed to</p> <p>25 Paracetamol During Development.</p>

<p>Page 86</p> <p>1 A. Right. I didn't include them 2 because I'm not looking at cerebral levels of 3 neurotransmitters. That's not what I was 4 asked to address. So I had no reason to 5 consider that literature.</p> <p>6 Q. Philippot, can you show me 7 where Evaluation of the Dentate Gyrus in 8 Adult Mice Exposed to Acetaminophen on 9 Postnatal Day 10 was considered?</p> <p>10 A. Sorry, which Philippot study 11 are you asking about, Adult Neurobehavioral 12 Alterations?</p> <p>13 Q. Evaluation of the Dendrite -- 14 well, I said Evaluation of the Dendrite Gyrus 15 in Adult Mice Exposed to Acetaminophen.</p> <p>16 A. Dentate gyrus. Yeah, I cite 17 two other studies with Philippot as the first 18 author. That one is not on the list because 19 I'm -- I was not asked to address anything 20 about the dentate gyrus. It wasn't relevant 21 to the questions I was asked to address, so 22 of course it wasn't in my materials 23 considered.</p> <p>24 Q. How about Suda, Therapeutic 25 Doses of Acetaminophen with Co-Administration</p>	<p>Page 88</p> <p>1 But there's no reason why I 2 would have a comprehensive evaluation of many 3 studies like this looking at ghrelin or 4 IL-1-beta because those are things that I was 5 not asked to address.</p> <p>6 Q. You have dozens of pieces of 7 literature on your materials considered list 8 that have nothing to do with the actual issue 9 you were asked to address though, right?</p> <p>10 A. As I stated, I reviewed some 11 additional literature that -- to get context 12 and background for the case overall.</p> <p>13 Q. Not just some, dozens, right?</p> <p>14 MR. COHEN: He wasn't finished. 15 Please let him finish his answer.</p> <p>16 A. So there -- yes, there may be 17 pieces of data, but again, there's no reason 18 why I would have a comprehensive search for 19 additional pieces of data like this, you 20 understand, because these are not what I was 21 asked to address.</p> <p>22 BY MR. JANUSH:</p> <p>23 Q. Admittedly, I find it 24 interesting that rodent studies were not what 25 you were asked to address, and the reason is</p>
<p>Page 87</p> <p>1 of Cysteine and Mannitol During Early 2 Development Result in Long-Term Behavioral 3 Changes in Laboratory Rats? 4 Didn't consider that, right?</p> <p>5 A. I don't have Suda on my list.</p> <p>6 Q. How about Philippot, 7 Paracetamol (Acetaminophen) and its Effect on 8 the Developing Mouse Brain? 9 Is that on your list?</p> <p>10 A. It is not one of the Philippot 11 studies that I cited -- or that I considered, 12 excuse me.</p> <p>13 Q. How about Herrington, Elevated 14 Ghrelin Alters the Behavioral Effects of 15 Perinatal Acetaminophen Exposure in Rats? 16 Is that in your list, 17 Herrington, of considered materials?</p> <p>18 A. Herrington. No, again, they're 19 looking at ghrelin levels, not something I 20 was asked to address. There may be studies 21 on my materials considered list that are not 22 directly relevant to the questions that I was 23 asked to address, but that's because I looked 24 at some literature just for background and 25 context of the whole question at hand.</p>	<p>Page 89</p> <p>1 because it's not easy to test for 2 neurodevelopmental in utero outcomes without 3 turning to animal models, right?</p> <p>4 MR. COHEN: Object to form.</p> <p>5 A. So to clarify, it's not that I 6 did not include animal studies. We do have 7 animal -- I did consider animal studies in my 8 report. For example, the animal studies that 9 show that massive overdoses of acetaminophen 10 do not cause evidence of NAPQI formation in 11 the brain.</p> <p>12 BY MR. JANUSH:</p> <p>13 Q. We'll get into that later.</p> <p>14 MR. COHEN: Please let him 15 finish.</p> <p>16 A. Can you restate the second part 17 of your question? There was something 18 additional I wanted to point out. Oh, that 19 was it.</p> <p>20 You were asking about it's 21 difficult to look at effects in utero without 22 using animal models. My response to that 23 would be, well, plaintiffs' experts have 24 relied on many studies that used, for 25 example, cell culture models that also</p>

<p style="text-align: right;">Page 90</p> <p>1 absolutely cannot model in utero exposure, 2 among other pieces of data that have no 3 relevance for in utero exposure. 4 BY MR. JANUSH: 5 Q. If you were in a hearing before 6 Judge Cote in this case and the judge 7 overseeing this case asked you why you failed 8 to mention in your report 23 of the 26 rodent 9 studies addressed by Dr. Pearson, how would 10 you respond to Judge Cote? 11 MR. COHEN: Object to the form. 12 A. As I've already said, these 13 papers are not addressing the issues that I 14 was asked to address, so there's no 15 particular reason why I should have a list -- 16 why I should have included these additional 17 studies. 18 MR. COHEN: Mr. Janush, at a 19 reasonable point can we take a break? 20 We've been going way over an hour. 21 MR. JANUSH: We can take a 22 break right now. 23 MR. COHEN: Whatever is 24 convenient for you. 25 MR. JANUSH: I can keep going.</p>	<p style="text-align: right;">Page 92</p> <p>1 University of Kansas. Right. 2 Who was your research advisor? 3 A. A person named Hartmut 4 Jaeschke. 5 Q. Hartmut Jaeschke? 6 A. Correct. 7 Q. Has Hartmut Jaeschke been a 8 significant mentor in your academic career? 9 A. He was my PhD mentor. I stayed 10 with him briefly as a postdoc fellow as well. 11 Q. Have you also published a great 12 deal with Hartmut Jaeschke? 13 A. I guess it defines [sic] on 14 your definition of a great deal. We have 15 published a number of papers together. 16 Q. Approximately how many? 17 A. Oh, boy. Off the top of my 18 head, I don't recall. I would -- I would 19 guess in the ballpark of 60. 20 Q. Indeed, Professor Jaeschke 21 suggested you should be an expert in this 22 case; is that true? 23 MR. COHEN: Object to the form. 24 A. No, he did not. Not to my 25 knowledge, no.</p>
<p style="text-align: right;">Page 91</p> <p>1 It's your call. 2 MR. COHEN: Okay. Let's take a 3 break. 4 THE VIDEOGRAPHER: We're going 5 off the record. The time is 10:04. 6 (Recess taken, 10:04 a.m. to 7 10:21 a.m. CDT) 8 THE VIDEOGRAPHER: We're going 9 back on record. The time is 10:21. 10 BY MR. JANUSH: 11 Q. Dr. McGill, when you received 12 your doctor of toxicology and pharmacology at 13 the University of Kansas, who was your 14 research advisor in your doctorate program? 15 A. Just a point of clarity, my 16 doctorate is in -- technically in toxicology, 17 although as I mentioned, it did include 18 pharmacology training. 19 My research advisor -- sorry. 20 Q. What's your doctorate in? I -- 21 A. Toxicology. Sorry, toxicology. 22 Q. Right. What did I say? 23 A. You said pharmacology. 24 Q. Sorry. I meant to say -- 25 sorry -- doctor of toxicology at the</p>	<p style="text-align: right;">Page 93</p> <p>1 BY MR. JANUSH: 2 Q. None of the literature you 3 published with Hartmut Jaeschke concerns the 4 study of acetaminophen and its potential 5 causal nexus with fetal neurodevelopmental 6 disorders, right? 7 A. I'm sorry, bit of a long 8 question, so I just want to make sure I'm 9 considering it. 10 Q. I'll shrink it. 11 Did you study fetal 12 neurodevelopmental disorders with Hartmut 13 Jaeschke that led to publications? 14 A. Again, my expertise and 15 training are not in neurodevelopment, so no, 16 I've not published on that with Hartmut or 17 otherwise, other than what we've addressed in 18 our review and what we've -- what I've 19 published that's relevant to this -- the 20 questions that I'm considering in this case. 21 Q. Would you agree that experts 22 should ensure objectivity of their research 23 and publications? 24 MR. COHEN: Object to form. 25 A. I -- yeah, I agree that you</p>

<p style="text-align: right;">Page 94</p> <p>1 should be as objective as possible. I have 2 to think how to frame this. You're always 3 guided -- well, I shouldn't say guided. 4 You're always testing a 5 hypothesis, right, and how you -- as I 6 mentioned with the scientific method, you 7 have your hypothesis, you make predictions 8 based on that, and then you test them. You 9 should be objective in your testing and in 10 your evaluation of the results of the 11 testing, yes. 12 BY MR. JANUSH: 13 Q. How many scientific 14 publications did you author with Hartmut 15 Jaeschke that were funded by grants from 16 McNeil Pharmaceuticals, the former corporate 17 entity that made and sold Tylenol? 18 MR. COHEN: Object to form. 19 Go ahead. 20 A. So when I was -- I'll start by 21 saying I don't know all of Hartmut's funding 22 history, all the details, right? It 23 didn't -- how to say that -- I was not a 24 recipient of any of those funds, so I guess I 25 have no reason to be familiar with all those</p>	<p style="text-align: right;">Page 96</p> <p>1 are a coauthor on with Hartmut Jaeschke; is 2 that right? 3 A. Yes. 4 Q. And if you look at the screen, 5 I've had our technician pull up: This 6 investigation was supported in part by grants 7 from McNeil Consumer Health to HJ and DR. 8 Do you see that? 9 MR. COHEN: I'm sorry. What 10 page is that on? 11 A. Yeah, I -- 12 MR. JANUSH: So the funding 13 acknowledgement is -- 14 MR. COHEN: I found it. Thank 15 you. Page 8. 16 BY MR. JANUSH: 17 Q. So do you see that on the 18 screen, this investigation was supported in 19 part by grants from McNeil Consumer 20 Health Inc.? 21 A. I see that, that it was 22 supported in part by grants from McNeil 23 Consumer Health to Hartmut and Dr. Rollins -- 24 I'm sorry, Dr. Jaeschke and Dr. Rollins. 25 Q. But when a company like McNeil</p>
<p style="text-align: right;">Page 95</p> <p>1 details. 2 There were -- as I recall, when 3 I was working in his laboratory, he did have 4 some funding from McNeil, which I -- I 5 believe is a -- basically J&J or associated 6 with J&J. I think there were maybe three, 7 four studies that -- for which Hartmut 8 received some support from that entity. 9 BY MR. JANUSH: 10 Q. Okay. You said you wouldn't 11 have reason to know what Hartmut received 12 funding on from McNeil or J&J. Let's turn to 13 your footnote 24, reference citation 85, 14 Exhibit 803. I'm just going to make it easy 15 on you by handing it over to you. 16 (Whereupon, Deposition 17 Exhibit P803, Plasma and Liver 18 Acetaminophen-Protein Adduct Levels in 19 Mice after Acetaminophen Treatment: 20 Dose-Response, Mechanisms, and 21 Clinical Implications, by McGill 22 et al., was marked for 23 identification.) 24 BY MR. JANUSH: 25 Q. This is a publication that you</p>	<p style="text-align: right;">Page 97</p> <p>1 that made and sold Tylenol at that time is 2 sponsoring a coauthor of yours, that aids in 3 the publication getting published, correct? 4 MR. COHEN: Object to the form. 5 BY MR. JANUSH: 6 Q. In other words, grant money 7 helps scientists fund studies, true? 8 A. Science is an expensive 9 endeavor. It requires funds for sure. 10 Q. And so in your report, you have 11 an area where you disclose ongoing funding 12 for studies and funding for past studies; is 13 that right? 14 A. I believe I did. 15 Q. You don't list this study, 16 right? 17 A. No, because I did not receive 18 any funding for this study. 19 Q. So is the standard that you 20 wouldn't list funding because you personally 21 weren't the grant recipient and it was one of 22 your coauthors? 23 A. Well, may -- can you please 24 tell me the page number in my report -- 25 Q. Sure.</p>

<p style="text-align: right;">Page 98</p> <p>1 A. -- that you're looking at.</p> <p>2 Q. I think it's --</p> <p>3 A. I don't want to waste</p> <p>4 everybody's time by flipping through here</p> <p>5 trying to remember where I put it.</p> <p>6 Q. I think it's PDF page 113 to</p> <p>7 115, so that will help us a bunch on the</p> <p>8 actual report, Exhibit 801. It's hard to</p> <p>9 follow your report. It changes pagination.</p> <p>10 A. I'm sorry. Yes, right, that's</p> <p>11 what I was saying, yes.</p> <p>12 Q. So it's page 11 of --</p> <p>13 A. Page 11?</p> <p>14 Q. -- your listed work.</p> <p>15 MR. COHEN: I apologize,</p> <p>16 Counsel. Are you talking about his</p> <p>17 report or his CV?</p> <p>18 MR. JANUSH: Well, his CV is</p> <p>19 appended to his report. That's how it</p> <p>20 was served. So it's an appendix to</p> <p>21 the report.</p> <p>22 THE WITNESS: Yeah, I think</p> <p>23 this is the source of the confusion.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. You have -- at page 5, you have</p>	<p style="text-align: right;">Page 100</p> <p>1 some funds from McNeil. Again, I point out</p> <p>2 that I am not a recipient of any of those</p> <p>3 funds, nor have I ever received, prior to</p> <p>4 this litigation -- my involvement in this</p> <p>5 litigation, have never received any sort of</p> <p>6 funds from J&J.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. Let's go to the next reference</p> <p>9 citation. It's on the page before. It's</p> <p>10 reference citation 79 and it's Exhibit P804.</p> <p>11 (Whereupon, Deposition</p> <p>12 Exhibit P804, Apoptosis or Necrosis in</p> <p>13 Acetaminophen-Induced Acute Liver</p> <p>14 Failure? New Insights From Mechanistic</p> <p>15 Biomarkers, by McGill et al., was</p> <p>16 marked for identification.)</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. Here's the first page of what I</p> <p>19 was able to get.</p> <p>20 MR. COHEN: And just for</p> <p>21 clarification, Counsel, on the</p> <p>22 record -- when you say "on the</p> <p>23 report," you're now looking at his --</p> <p>24 and putting up on the screen pages</p> <p>25 from his curriculum vitae.</p>
<p style="text-align: right;">Page 99</p> <p>1 Research, Journal Publications (latest to</p> <p>2 earliest).</p> <p>3 That's why I think we should go</p> <p>4 to the screen and pull up P801 and go to</p> <p>5 page 113, and at PDF page 113, the first</p> <p>6 reference citation -- well, we can look at --</p> <p>7 I believe it's the next page is reference</p> <p>8 citation 85. And that's the report. That</p> <p>9 matches the title.</p> <p>10 You see that, Plasma and liver</p> <p>11 acetaminophen-protein adduct levels in mice</p> <p>12 after acetaminophen treatment?</p> <p>13 A. I see it.</p> <p>14 Q. So here is a study with Hartmut</p> <p>15 Jaeschke and you and others addressing plasma</p> <p>16 and liver acetaminophen-protein adduct levels</p> <p>17 in mice after acetaminophen treatment</p> <p>18 sponsored by the makers and sellers of</p> <p>19 Tylenol, right?</p> <p>20 MR. COHEN: Object to the form.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. At least sponsored as to your</p> <p>23 coauthor, Hartmut Jaeschke, correct?</p> <p>24 MR. COHEN: Object to the form.</p> <p>25 A. Hartmut, Dr. Jaeschke, received</p>	<p style="text-align: right;">Page 101</p> <p>1 MR. JANUSH: Yes, that is --</p> <p>2 was appended as an exhibit to his</p> <p>3 report.</p> <p>4 MR. COHEN: I understand that.</p> <p>5 MR. JANUSH: It was served as</p> <p>6 one document, one PDF, and so that's</p> <p>7 how I'm referring to it.</p> <p>8 BY MR. JANUSH:</p> <p>9 Q. And here we're addressing</p> <p>10 again --</p> <p>11 MR. JANUSH: You can go back to</p> <p>12 where you were, David.</p> <p>13 BY MR. JANUSH:</p> <p>14 Q. We'll call it on the screen so</p> <p>15 you can see it easier. Here too is a callout</p> <p>16 for McNeil funding. Dr. Jaeschke received</p> <p>17 research grant supports from -- consulted for</p> <p>18 McNeil Consumer Health, sorry.</p> <p>19 Do you see that? Dr. Jaeschke</p> <p>20 consulted for McNeil Consumer Health with</p> <p>21 respect to this study?</p> <p>22 A. That's not the portion that's</p> <p>23 highlighted, but I see the statement.</p> <p>24 Q. Now it's being highlighted. Do</p> <p>25 you see that now that it's highlighted?</p>

<p style="text-align: right;">Page 102</p> <p>1 A. Yes.</p> <p>2 Q. So that's not just grant</p> <p>3 support. This is your coauthor consulting</p> <p>4 for McNeil Consumer Health within the</p> <p>5 confines of this particular publication,</p> <p>6 right?</p> <p>7 MR. COHEN: Object to the form.</p> <p>8 BY MR. JANUSH:</p> <p>9 Q. That's what that disclosure is,</p> <p>10 right?</p> <p>11 A. No, that's --</p> <p>12 MR. COHEN: Object to form.</p> <p>13 A. That's an inaccurate statement.</p> <p>14 In this particular case, there's no statement</p> <p>15 of research support for this publication.</p> <p>16 Dr. Jaeschke -- or my</p> <p>17 interpretation -- my read of this, based on</p> <p>18 my career of experience in this field, is</p> <p>19 that he's just being extra cautious and</p> <p>20 pointing out, by the way, I've received -- or</p> <p>21 he has consulted for McNeil Consumer Health.</p> <p>22 BY MR. JANUSH:</p> <p>23 Q. It's called a conflict of</p> <p>24 interest disclosure, right?</p> <p>25 A. It's a conflict of interest</p>	<p style="text-align: right;">Page 104</p> <p>1 supported in part by grants from McNeil</p> <p>2 Consumer Health to Hartmut Jaeschke and to</p> <p>3 Steven C. Curry?</p> <p>4 And you can look at the screen.</p> <p>5 I'm trying to speed it along for you.</p> <p>6 MR. COHEN: Well, no, he's</p> <p>7 entitled to look at the --</p> <p>8 MR. JANUSH: You are absolutely</p> <p>9 entitled to look at the document, but</p> <p>10 we're also calling it up in real time</p> <p>11 to make it easy for you.</p> <p>12 A. I see the -- that the statement</p> <p>13 says that. Again, grants from McNeil</p> <p>14 Consumer Health to Hartmut and Dr. Curry</p> <p>15 apparently.</p> <p>16 BY MR. JANUSH:</p> <p>17 Q. And we'll go to your footnote 2</p> <p>18 from your report, which is also reference</p> <p>19 citation 94. This is P806.</p> <p>20 (Whereupon, Deposition</p> <p>21 Exhibit P806, The mechanism underlying</p> <p>22 acetaminophen-induced hepatotoxicity</p> <p>23 in humans and mice involves</p> <p>24 mitochondrial damage and nuclear DNA</p> <p>25 fragmentation, by McGill et al., was</p>
<p style="text-align: right;">Page 103</p> <p>1 disclosure in which you report anything that</p> <p>2 could be perceived by someone as a potential</p> <p>3 conflict.</p> <p>4 Q. Okay.</p> <p>5 A. But again, this is not support</p> <p>6 for that article, and again, it has nothing</p> <p>7 to do with me.</p> <p>8 Q. Let's go to reference citation</p> <p>9 77, Exhibit P805.</p> <p>10 (Whereupon, Deposition</p> <p>11 Exhibit P805, Circulating</p> <p>12 Acylcarnitines as Biomarkers of</p> <p>13 Mitochondrial Dysfunction after</p> <p>14 Acetaminophen Overdose in Mice and</p> <p>15 Humans, by McGill et al., was marked</p> <p>16 for identification.)</p> <p>17 A. Thank you.</p> <p>18 BY MR. JANUSH:</p> <p>19 Q. Circulating Acylcarnitines as</p> <p>20 Biomarkers of Mitochondrial Dysfunction with</p> <p>21 Acetaminophen Overdose in Mice and Humans.</p> <p>22 You are a coauthor with Hartmut Jaeschke,</p> <p>23 amongst others, right?</p> <p>24 A. Correct.</p> <p>25 Q. And here too, was this also</p>	<p style="text-align: right;">Page 105</p> <p>1 marked for identification.)</p> <p>2 BY MR. JANUSH:</p> <p>3 Q. And this is: The mechanism</p> <p>4 underlying acetaminophen-induced</p> <p>5 hepatotoxicity in humans and mice involves</p> <p>6 mitochondrial damage and nuclear DNA</p> <p>7 fragmentation.</p> <p>8 Do you see that?</p> <p>9 A. Yes.</p> <p>10 Q. And on the very bottom of the</p> <p>11 first page -- you don't have to go far. You</p> <p>12 don't have to flip through this one.</p> <p>13 A. The first page.</p> <p>14 Q. On the bottom left-hand corner,</p> <p>15 conflict of interest, Steven C. Curry and</p> <p>16 Hartmut Jaeschke are supported by grants from</p> <p>17 McNeil Consumer Health.</p> <p>18 Do you see that?</p> <p>19 A. I see it.</p> <p>20 Q. So here too, two of your study</p> <p>21 authors were funded by the makers and sellers</p> <p>22 of Tylenol, right?</p> <p>23 MR. COHEN: Object to the form.</p> <p>24 A. Based on this statement,</p> <p>25 Dr. Curry and Dr. Jaeschke have received</p>

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1 grants from McNeil.
 2 BY MR. JANUSH:
 3 Q. Is that a "yes" to my question?
 4 MR. COHEN: Object to form.
 5 A. Well, my answer is that
 6 apparently Dr. Curry, as well as Dr.
 7 Jaeschke, have received grants from McNeil.
 8 That's what the statement says.
 9 BY MR. JANUSH:
 10 Q. Just to be clear, I want to
 11 make sure I'm getting this right: Your
 12 standard in not disclosing grants from
 13 McNeil, the maker and seller of Tylenol under
 14 the J&J family of companies, was because you
 15 specifically were attenuated from that grant,
 16 right? It wasn't monies given to you
 17 directly?
 18 A. I'm sorry.
 19 Q. Just to your coauthors, right?
 20 MR. COHEN: Object to the form.
 21 Go ahead.
 22 A. Sorry. Where did I not
 23 disclose? What are you referring to?
 24 BY MR. JANUSH:
 25 Q. Well --

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1 A. It is disclosed in these
 2 publications.
 3 Q. You have a section in your
 4 report, right, and it's entitled -- I'll take
 5 you to it. It's at page 20 of your CV.
 6 A. Is this -- okay.
 7 Q. Extramural funding.
 8 A. Yes.
 9 Q. Page 20, starts at the very
 10 bottom of page 20, extramural funding, way
 11 back like the fourth-to-last page of the
 12 entire PDF of your expert report.
 13 A. Yes.
 14 Q. That extramural funding,
 15 studies are listed, right?
 16 A. Well, extramural sources of
 17 funding for my research are listed.
 18 Q. Right.
 19 A. For research in my laboratory.
 20 Q. Okay. So when -- and then
 21 there's another area that addresses
 22 intramural funding, right?
 23 A. Yes, I believe there is a
 24 section on intramural funding.
 25 Q. But with respect to extramural

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1 funding for your laboratory, you had no
 2 problem listing when you are in the role of,
 3 quote, other personnel on a laudatory grant
 4 of \$4,278,884 from the National Institutes of
 5 Health with James as the PI, right? Here,
 6 you're not the PI on that, right?
 7 A. Right.
 8 Q. It's at the bottom of page 21.
 9 I want to make sure you're looking -- middle
 10 of page 21. I want to make sure you're
 11 looking at it with me. It's also up on the
 12 screen.
 13 A. No, I'm not the PI. "Other
 14 personnel" is not a general term. It's an
 15 official category with the National
 16 Institutes of Health. I'm listed as --
 17 officially listed as -- in that official
 18 category of other personnel, and I receive
 19 salary support for it.
 20 Q. Okay.
 21 A. So in that sense, I -- this is
 22 one of my projects.
 23 Q. And then on the next one, you
 24 also had no problem listing -- literally, the
 25 very next one, yep, KO1 DK126990, National

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1 Institutes of Health, Lutkewitte is the PI.
 2 I'm sure I'm pronouncing that name wrong, but
 3 that's who the PI is on this study with a
 4 grant of \$521,314, right?
 5 A. That's correct. So again, what
 6 is typical to list on your CV is when you are
 7 a named individual on that grant. Otherwise,
 8 you know, if I were to list myself as a grant
 9 on Dr. Jaeschke's McNeil funding -- sorry,
 10 list myself as personnel in any capacity on
 11 Dr. Jaeschke's McNeil funding, that would be
 12 unethical because this is a presentation of
 13 my work, and others in my field would see it
 14 as me taking some credit for his work.
 15 MR. JANUSH: Move to strike,
 16 nonresponsive. I didn't have a
 17 question pending for you to answer.
 18 BY MR. JANUSH:
 19 Q. At the bottom of that, I see:
 20 Effort, colon, 0% FTE. So on this one,
 21 \$521,314 grant not provided by McNeil, you
 22 had 0% FTE. Explain what FTE is.
 23 A. FTE stands for full-time
 24 equivalent.
 25 Q. So what does this mean, 0%

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1 full-time equivalent?

2 A. Yeah, so what it means is that

3 I was in an official named capacity on this

4 grant as other personnel, but I declined any

5 salary recovery from it. This was a -- this

6 was a type of training grant, it's a KL1.

7 Dr. Lutkewitte was a postdoc along with

8 myself at Washington University in St. Louis.

9 He obtained this grant as PI, but a component

10 of the grant is mentoring.

11 And so he asked me, as I was a

12 bit ahead in my career, if I would be willing

13 to mentor him. And I said yes because I

14 believe that's a very important thing to do,

15 mentor young scientists, and I did not feel

16 that I should take any salary recovery from

17 it.

18 Nevertheless, I was an

19 officially named person in the grant, which

20 is why I've included it in here.

21 Q. And similarly, when a coauthor

22 gets grant money from the makers and sellers

23 of Tylenol to publish science related to

24 Tylenol and neurotoxic issues, that advances,

25 as a whole, the entire publication, right?

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1 MR. COHEN: Object to the form.

2 BY MR. JANUSH:

3 Q. In other words, when one

4 scientist receives grant money from the maker

5 and seller of Tylenol, that has the benefit

6 of aiding the entire work, right?

7 MR. COHEN: Object to the form.

8 A. Again, science is an expensive

9 endeavor. You need funds to do it. There

10 are -- I mean, it helps you to pay for things

11 like pipette tips, tubes, things that are

12 necessary to do -- to complete the project.

13 It doesn't benefit -- well,

14 with respect to Dr. Jaeschke's funding, I was

15 not a recipient, never benefited me

16 personally, other than helping him pay for

17 the pipette tips that I was using.

18 BY MR. JANUSH:

19 Q. Marking 807, Plaintiffs'

20 Exhibit 807.

21 (Whereupon, Deposition

22 Exhibit P807, Webpage, Johnson &

23 Johnson Acquires McNeil Laboratories,

24 was marked for identification.)

25 ///

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1 BY MR. JANUSH:

2 Q. This is a screenshot

3 from Johnson & Johnson, Our Story. The

4 Johnson & Johnson Company Timeline. 1959,

5 Johnson & Johnson acquires McNeil

6 Laboratories. And it says: At the heart of

7 its business -- at the bottom, I'm reading

8 three lines from the bottom -- at the heart

9 of its business was Tylenol, the first

10 aspirin-free pain reliever. Today, Tylenol

11 remains a household name and one of Johnson &

12 Johnson's most popular products.

13 Do you see that?

14 A. I see it.

15 MR. COHEN: Object to the --

16 just note my objection to the use of

17 this exhibit.

18 Go ahead.

19 BY MR. JANUSH:

20 Q. When you were working on

21 studies that were funded in part by McNeil to

22 one of your coauthors, did you have an

23 appreciation that at that time that it was

24 McNeil, the maker and seller of Tylenol?

25 MR. COHEN: Object to the form.

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1 A. As I stated in my previous

2 answer, yeah, I'm aware that McNeil -- I

3 don't know exactly their relationship, but I

4 know -- I think I said earlier, McNeil

5 basically is J&J, so...

6 BY MR. JANUSH:

7 Q. I didn't say "at that time" in

8 that prior question, so I modified this

9 question.

10 A. Okay.

11 Q. Did you know then, when you

12 were publishing your work, that McNeil was

13 paying Dr. Jaeschke grant money to publish

14 that article with you?

15 MR. COHEN: Object to the form.

16 A. I knew Dr. Jaeschke had grant

17 funding from McNeil, and -- and yes, that

18 McNeil was part of Johnson & Johnson.

19 BY MR. JANUSH:

20 Q. And that McNeil was the maker

21 and seller of Tylenol?

22 A. I'm aware, yeah.

23 Q. And you were aware then too?

24 A. Yes.

25 Q. Okay. And --

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1 A. In the United States.

2 Q. And while serving as an expert
3 in this case, concerning this all-important
4 product to Johnson & Johnson -- it's one of
5 its most popular products according to the
6 web page -- it didn't occur to you that it
7 might be a wise thing to let Judge Cote and
8 the plaintiffs know that four of your
9 publications with Hartmut Jaeschke were
10 sponsored in part by the defendant?

11 MR. COHEN: Objection. That's
12 just inappropriate.

13 MR. JANUSH: You may answer.

14 A. I never received any funding of
15 any form from McNeil or Johnson & Johnson
16 prior to this, my involvement in this
17 litigation. I can't speak to Hartmut's full
18 funding history. I'm aware he had some
19 funding from McNeil.

20 BY MR. JANUSH:

21 Q. Did you know that as recent as
22 2020, your mentor, your former research
23 advisor in your PhD program, and your
24 coauthor on, as you put it, approximately 60
25 publications, was communicating with

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1 senior -- a senior scientist at Janssen
2 research and development to help the
3 Johnson & Johnson companies counter published
4 literature linking fetal acetaminophen
5 exposure to ADHD?

6 Did you know that?

7 MR. COHEN: Objection. Object
8 to the form.

9 A. No. No, I had no knowledge of
10 that.

11 BY MR. JANUSH:

12 Q. Incidentally, do you know how
13 many times you've cited -- let me ask it
14 differently.

15 Did you know that you cited
16 Dr. Jaeschke within the body of your expert
17 report and the appendices to your report 141
18 times?

19 MR. COHEN: Object to the form.

20 A. Did I know that I did that?
21 No. I mean, I don't know the number of
22 times.

Confidential Subject to Protective Order

<p>Page 118</p> <p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>

<p>Page 122</p> <p>[REDACTED]</p>	<p>Page 124</p> <p>1 going to do something else.</p> <p>2 Dr. McGill, have you reviewed</p> <p>3 any studies that concluded that biological</p> <p>4 causation between acetaminophen and fetal</p> <p>5 exposure -- or between fetal exposure of</p> <p>6 acetaminophen and neurodevelopmental outcomes</p> <p>7 are biologically impossible?</p> <p>8 MR. COHEN: Object to form.</p> <p>9 A. I'm sorry, can you ask the</p> <p>10 question again.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. Have you reviewed any studies</p> <p>13 concluding that acetaminophen in utero</p> <p>14 exposure and resulting neurodevelopmental</p> <p>15 outcomes are biologically impossible?</p> <p>16 MR. COHEN: Object to form.</p> <p>17 A. So to be clear, I was not asked</p> <p>18 to address the neurodevelopmental outcomes or</p> <p>19 anything -- behavioral outcomes, anything</p> <p>20 similar to that.</p> <p>21 What I have reviewed in my</p> <p>22 literature and stated -- or described in my</p> <p>23 expert report are a number of studies which</p> <p>24 together demonstrate that there is no</p> <p>25 formation of NAPQI in the brain, which is the</p>
<p>14 Dr. McGill, I'm going to go</p> <p>15 through really briefly your summary opinions</p> <p>16 that are up front in your report that you get</p> <p>17 into in greater detail later.</p> <p>18 So this is at page 6 of the</p> <p>19 report.</p> <p>20 A. It doesn't appear to be page 6.</p> <p>21 Q. My apologies.</p> <p>22 A. If you're referring to -- I</p> <p>23 think it was paragraph 4, as we discussed</p> <p>24 earlier, if that's what you're referring to.</p> <p>25 Q. Actually, you know what? I'm</p>	<p>Page 125</p> <p>1 question that I was asked to address and that</p> <p>2 the plaintiffs opine is a mechanism for such</p> <p>3 neurodevelopmental or behavioral outcomes.</p> <p>4 MR. JANUSH: Move to strike as</p> <p>5 nonresponsive everything after "I was</p> <p>6 not asked to review -- address the</p> <p>7 neurodevelopmental outcomes or</p> <p>8 anything -- behavioral outcomes,</p> <p>9 anything similar to that." Everything</p> <p>10 following those words, move to strike.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. Dr. McGill, have you made an</p> <p>13 effort to accurately reflect your</p> <p>14 understanding of what each scientific piece</p> <p>15 of literature that you relied on actually</p> <p>16 addressed in the papers you cited?</p> <p>17 A. Yes. The papers that I</p> <p>18 reviewed in my expert report, I've made my</p> <p>19 best effort to be accurate.</p> <p>20 Q. Because if you inaccurately</p> <p>21 cite a paper you relied on, it is possible</p> <p>22 you misunderstood what the paper stood for,</p> <p>23 right?</p> <p>24 MR. COHEN: Object to the form.</p> <p>25 ///</p>

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1 BY MR. JANUSH:
 2 Q. Hypothetically.
 3 A. Hypothetically? If -- if
 4 one -- I suppose if one summarized a study or
 5 described a study incorrectly, it's possible
 6 that they misunderstood or missed something.
 7 Q. It's either a misunderstanding
 8 or it's a purposeful error, right?
 9 MR. COHEN: Object to the form.
 10 BY MR. JANUSH:
 11 Q. When someone inaccurately cites
 12 a paper that they rely on?
 13 MR. COHEN: Object to the --
 14 A. No, it could also just be an
 15 honest error that is not the result of
 16 misunderstanding, or could be something
 17 that's overlooked, some sort of accidental --
 18 so the answer to your question is no.
 19 BY MR. JANUSH:
 20 Q. Let's turn to page 7 -- or
 21 excuse me, paragraph 7 of your report. And
 22 it's at paragraph 7 that you are addressing
 23 different studies you've been involved in
 24 focused on acetaminophen, fair?
 25 A. It's describing certain things

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1 that I considered major foci of my research
 2 career that I, you know -- yeah.
 3 Q. And the majority of the studies
 4 that are addressed at paragraph 7 concern
 5 single-dose overdose of acetaminophen being
 6 studied, right?
 7 A. With the caveat that they
 8 sometimes involve overdose patients, and
 9 overdose patients, it's very difficult to
 10 determine what form their overdose took.
 11 Q. And one of the studies that you
 12 address concerned whether acetaminophen could
 13 cause hearing loss, right? We talked about
 14 that earlier?
 15 A. Correct.
 16 Q. And you found that a large
 17 single overdose of acetaminophen did not lead
 18 to NAPQI formation in the cochlea within the
 19 ear of mice, right?
 20 A. Correct.
 21 Q. And by citing to this study,
 22 Dr. McGill, were you seeking to imply that an
 23 acetaminophen overdose study looking at the
 24 cochlea is relevant to the in utero
 25 developing fetal brain?

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1 A. No, I never made such a
 2 statement. It is interesting to note that
 3 the cochlea contain neurons, and we're
 4 talking about the brain, and the parenchymal
 5 or major cell type of the brain is neurons,
 6 but I never made the statement that you're
 7 saying.
 8 Q. And on page 5 in the middle of
 9 the page, you address a 2012 publication and
 10 you say, quote: In 2012, we published the
 11 first evidence that mitochondrial damage also
 12 occurs --
 13 Excuse me, I want to read below
 14 it. I apologize.
 15 In 2012, we published a
 16 comparison of hepatic acetaminophen-protein
 17 binding, glutathione and oxidative stress in
 18 mice and rats, the latter species being much
 19 less susceptible to liver toxicity from
 20 acetaminophen overdose. The results indicate
 21 that NAPQI must bind to mitochondrial
 22 proteins to cause toxicity.
 23 Did I read that right?
 24 A. Yes.
 25 Q. Would you agree that

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1 mitochondrial dysfunction is critical for the
 2 development of necrosis after APAP treatment?
 3 MR. COHEN: Object to form.
 4 A. It's a critical feature of
 5 liver injury due to acetaminophen overdose.
 6 Specifically, yeah, overdose.
 7 With the caveat that
 8 mitochondrial dysfunction is not an
 9 irreversible phenomenon. It can occur
 10 without subsequent injury.
 11 BY MR. JANUSH:
 12 Q. Now, when we address that
 13 paragraph I just read, we see footnote 3 at
 14 the end of the sentence, right?
 15 A. Yes.
 16 Q. And here you are citing to your
 17 own publication at footnote 3, right?
 18 A. The publication described in
 19 that paragraph, yes.
 20 Q. Right.
 21 Did you know, by the way, that
 22 you cited to your own publications 12 times
 23 within the first 12 pages and within the
 24 first 24 citations to your expert report?
 25 A. I wasn't aware of the number,

<p style="text-align: right;">Page 130</p> <p>1 but I would like to add that I'm spending 2 much of the first 12 pages describing my 3 career and achievement, so of course I'm 4 going to cite myself. 5 In addition to that, and again 6 in response to your question previously about 7 how many times I've cited Dr. Jaeschke, 8 acetaminophen toxicity is a relatively small 9 field. There are only a handful of experts. 10 Dr. Jaeschke is one of the leading experts. 11 I am also one of the leading experts. It's 12 difficult not to cite our -- my studies or 13 his studies. 14 Q. If you're studying the liver, 15 that's right, right? Correct? 16 A. We don't know that much 17 about -- well, let me rephrase that. 18 Toxicity in the liver, as well 19 as the kidney, those are the only two 20 well-characterized toxicities of 21 acetaminophen. And so -- I'm trying to 22 consider the best way to say this. 23 So the majority of research on 24 acetaminophen metabolism and toxicity has 25 been done in the liver, and so due to the</p>	<p style="text-align: right;">Page 132</p> <p>1 Q. How did you arrive at the 2 conclusion that NAPQI, quote, must bind, 3 quote, to mitochondrial proteins to cause 4 toxicity? 5 A. Yes, so there are multiple 6 sources of data for this, if you'd like me to 7 go into detail. So this idea originated from 8 older data from like 1980s, 1990s. There's a 9 regioisomer of acetaminophen that does not 10 cause liver injury in some models called 11 AMAP. That's -- so what has been observed is 12 that AMAP binds to proteins but does not 13 cause liver injury, and it's thought that 14 that's because if you compare what proteins 15 are bound between acetaminophen and AMAP in 16 some models, the NAPQI from acetaminophen, 17 reacting metabolite of acetaminophen, binds 18 specifically -- or binds more to 19 mitochondrial proteins. The reactive 20 metabolite of AMAP binds less to 21 mitochondrial proteins. 22 So that was kind of the initial 23 clue that it is probably mediated in part by 24 mitochondrial protein binding. 25 In addition to that, there are</p>
<p style="text-align: right;">Page 131</p> <p>1 paucity of data with other potential organ 2 toxicities, we have to rely on that, and, in 3 fact, the plaintiffs' experts also rely on 4 that when they proposed this idea that NAPQI 5 mediates the toxicity in the brain and 6 oxidative stress mediates the toxicity in the 7 brain. So we all have to rely on it just as 8 your experts did. 9 MR. JANUSH: Move to strike, 10 nonresponsive. 11 BY MR. JANUSH: 12 Q. You are a liver researcher 13 primarily, right? 14 MR. COHEN: Object to form. 15 BY MR. JANUSH: 16 Q. Just asking if -- background 17 information. It's a yes or a no. 18 A. The focus of my research is 19 threefold. So I study various aspects of 20 acetaminophen toxicity with a focus on 21 hepatotoxicity. I also study biomarkers of 22 drug-induced liver injury, including 23 acetaminophen toxicity, and we also look at 24 liver regeneration and repair after injury, 25 including after acetaminophen toxicity.</p>	<p style="text-align: right;">Page 133</p> <p>1 other models. For example, this paper in 2 this paragraph that you mentioned, footnote 3 3 on page 5 of my report, in that paper we 4 demonstrated that rats, which again, are very 5 resistant to acetaminophen hepatotoxicity, 6 have much lower mitochondrial protein binding 7 after an overdose of acetaminophen compared 8 to mice, which are sensitive to acetaminophen 9 hepatotoxicity. 10 In addition to that, if you 11 block NAPQI formation using P450 inhibitors, 12 then you don't get mitochondrial dysfunction. 13 So those are three key pieces 14 of data that contribute probably the most to 15 that statement, that underlie that statement. 16 There are some additional pieces of data as 17 well. 18 MR. JANUSH: I'm going to mark 19 what's been -- I'm providing what's 20 been marked as Plaintiffs' Exhibit 21 809. 22 (Whereupon, Deposition 23 Exhibit P809, Acetaminophen-induced 24 Liver Injury in Rats and Mice: 25 Comparison of Protein Adducts,</p>

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1 Mitochondrial Dysfunction, and
 2 Oxidative Stress in the Mechanism of
 3 Toxicity, by McGill et al., was marked
 4 for identification.)
 5 BY MR. JANUSH:
 6 Q. And this is a -- the study that
 7 you cite in your report at footnote 3.
 8 Do you see that? Can you
 9 confirm that? Acetaminophen-induced liver
 10 injury in rats and mice?
 11 A. Yes, that's the reference.
 12 Q. And here you are again
 13 publishing here with Dr. Hartmut Jaeschke,
 14 right?
 15 A. Correct.
 16 Q. And it's 2012.
 17 A. I believe that was the year it
 18 was published, yes.
 19 Q. And if we turn to page 4 of 19,
 20 we see a statement: Mitochondrial
 21 dysfunction is known to play a role in APAP
 22 hepatotoxicity in both mice and humans.
 23 A. Uh-huh. I'm sorry, can you
 24 tell me -- show me where you're looking at?
 25 MR. JANUSH: Yeah, I'll have

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1 David search. It's right here
 2 under -- there you are, David. You're
 3 there.
 4 A. Oh. Yes.
 5 BY MR. JANUSH:
 6 Q. And then after that statement,
 7 it says: It is well-established that NAPQI
 8 binds to mitochondrial proteins, citing to
 9 Tirmenstein and Nelson 1989.
 10 A. Uh-huh.
 11 Q. And it is generally accepted
 12 that this is an important early event in the
 13 mitochondrial dysfunction and associated
 14 oxidative stress seen after APAP overdose.
 15 A. Uh-huh.
 16 Q. Did I read that correctly?
 17 A. Yes.
 18 Q. And you believe in that today,
 19 right?
 20 A. With the caveat that in this
 21 paper we're talking about the liver.
 22 Q. And if we turn to page 6 of 19
 23 and search for the terms "protein binding,
 24 especially mitochondrial protein binding, is
 25 necessary for initiation of APAP toxicity" --

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1 MR. JANUSH: No, not there,
 2 David -- Michael. Sorry. I thought
 3 this was prehighlighted. I'll find
 4 it. It's at the bottom of the page,
 5 last paragraph. Protein binding,
 6 especially mitochondrial protein
 7 binding, is necessary for initiation
 8 of APAP toxicity.
 9 BY MR. JANUSH:
 10 Q. Do you see that?
 11 A. I see it, yes.
 12 Q. Do you hold that opinion today?
 13 A. That is what is known to --
 14 it's known that protein binding in the liver
 15 after an overdose, and particularly
 16 mitochondrial protein binding in the liver
 17 after an overdose, is necessary for
 18 initiation of APAP toxicity.
 19 APAP being acetaminophen, just
 20 for the record.
 21 Q. By the way, just while we're
 22 talking about for the record. For the
 23 record, the liver has the ability to
 24 regenerate. The brain does not have the
 25 ability to regenerate following injury,

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1 right?
 2 A. I -- again, I'm not a
 3 neuroscientist. I can't comment on brain
 4 regeneration. I have no reason -- well,
 5 yeah, I can't comment on brain regeneration.
 6 I don't know.
 7 Q. And all these studies that we
 8 are addressing in the beginning of your
 9 report at page 5 and thereafter, these are
 10 looking at liver cells, not brain cells,
 11 right?
 12 A. Okay. Can you -- I want to
 13 make sure, because --
 14 Q. Page 5, page 6.
 15 A. You're referring to all these
 16 studies in my report?
 17 Q. Other -- other than -- other
 18 than the cochlea study we've spoken about
 19 from 2015, I'm talking about page 5, the 2018
 20 research group addressing liver tissue at the
 21 bottom of page 6.
 22 A. Uh-huh.
 23 Q. Liver studies, right?
 24 MR. COHEN: So you want him to
 25 check his footnotes; is that what

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1 you're asking him?

2 MR. JANUSH: Nope. Nope. He

3 writes it in the body of the text.

4 If he needs help, he'll let me

5 know.

6 BY MR. JANUSH:

7 Q. It says liver.

8 A. You're asking specifically

9 pages 5 and 6, because there's some

10 additional on page --

11 Q. I'll walk you there on that.

12 I'm talking about pages 5 and 6, the

13 beginning of your report here.

14 These are liver studies, right,

15 except for the cochlea study?

16 MR. COHEN: Object to the form.

17 Just take your time and review

18 what he's asked you to review.

19 BY MR. JANUSH:

20 Q. I didn't ask you to review

21 anything. These are liver studies, right,

22 that you're addressing --

23 MR. COHEN: You're asking a

24 question based upon all of these

25 studies.

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1 A. So not exactly. So again,

2 there are actually two studies citing -- one

3 is the hearing loss study.

4 BY MR. JANUSH:

5 Q. It says that, yeah.

6 A. Another is drug metabolism in

7 the ear. So those are two studies. On

8 pages 5 and 6 the rest are dealing primarily

9 with liver injury, though I note on page 7 we

10 mention our review that --

11 Q. And on page 7, the top two

12 studies that are bulleted, those are also

13 liver studies, right?

14 A. The top two studies are

15 primarily concerned with liver injury and

16 repair, yeah.

17 Q. Okay. At page 5 of your

18 report, when you address the bullet: In

19 2013, we published a study of the

20 dose-response and kinetics of NAPQI formation

21 in the liver in mice, comparing hepatic

22 glutathione and hepatic and serum

23 acetaminophen-protein adducts with various

24 liver damage endpoints. The data demonstrate

25 that NAPQI formation correlates with liver

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1 injury.

2 You wrote that, right?

3 A. Yes.

4 [REDACTED]

5 [REDACTED]

6 [REDACTED]

7 [REDACTED]

8 [REDACTED]

9 [REDACTED]

10 A. Did we already have -- I

11 guess --

12 Q. It's 803. I believe I put that

13 before you already. Can you pull that up?

14 A. Yeah.

15 Q. Great.

16 In this study, you address that

17 toxicities might arise at doses below

18 hepatotoxic levels, true?

19 A. No.

20 Q. Well, let's look at the

21 abstract in the -- just in the abstract

22 alone, we will look at the following

23 language: Importantly, the data confirm --

24 it's in the middle, slightly down from

25 there -- importantly, the data confirm

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1 earlier work that showed that protein-derived

2 APAP-cysteine can appear in plasma without

3 liver injury.

4 Do you see that?

5 A. Yes. But protein adduct

6 formation is not toxicity, and you asked

7 about toxicity.

8 Q. Protein adduct formation is the

9 precursor to NAPQI, isn't it?

10 A. It's not a precursor to NAPQI,

11 no. NAPQI is formed by P450s and then reacts

12 with proteins. NAPQI is the precursor to

13 protein binding.

14 Q. So if NAPQI is the precursor to

15 protein binding, and here you're showing

16 protein-derived APAP-cysteine can appear in

17 plasma without liver injury, you're showing

18 that -- you're showing that protein binding

19 can occur without glutathione depletion in

20 this study, right?

21 A. So to answer your question

22 directly, let me -- what we show in the paper

23 is that protein binding can occur without

24 toxicity.

25 If you look at Figure 2A,

<p style="text-align: right;">Page 142</p> <p>1 Figure 2 on page 15 of the version that I</p> <p>2 have that you've provided. I'll just give</p> <p>3 you a moment.</p> <p>4 Q. Can you pull that up on the</p> <p>5 screen? There, it's up on the screen.</p> <p>6 A. Okay. Let me know when I can</p> <p>7 continue, please. Okay.</p> <p>8 Yeah, if you look at panel A</p> <p>9 there in Figure 2, this is total glutathione</p> <p>10 in the liver, so GSH plus GSSG, because it</p> <p>11 exists in two forms, so the total is a</p> <p>12 combination of both. You can see that every</p> <p>13 single dose we tested caused loss of</p> <p>14 glutathione.</p> <p>15 Q. If we go to page 2, what I want</p> <p>16 to address, following the introduction in the</p> <p>17 second paragraph, it says: Forty years ago,</p> <p>18 a series of critical papers established the</p> <p>19 mechanism of APAP-induced liver injury begins</p> <p>20 with the P450-catalyzed conversion of the</p> <p>21 drug to an electrophile that can react with</p> <p>22 glutathione, GSH, and bind to proteins.</p> <p>23 A. Uh-huh.</p> <p>24 Q. This reactive metabolite is</p> <p>25 generally believed to be</p>	<p style="text-align: right;">Page 144</p> <p>1 exclusively within hepatocytes, followed by</p> <p>2 secretion or exocytosis of some of the</p> <p>3 adducted proteins into plasma.</p> <p>4 Alternatively, NAPQI could</p> <p>5 diffuse out of the hepatocyte and bind to</p> <p>6 plasma proteins in situ. We decided to take</p> <p>7 an in vitro approach to test these</p> <p>8 hypotheses.</p> <p>9 Did I read that correctly?</p> <p>10 A. Yes, those were the hypotheses</p> <p>11 that we had at the time.</p> <p>12 Q. And then when we get to page 7,</p> <p>13 you address: It has long been believed that</p> <p>14 G -- extensive GSH -- that's glutathione,</p> <p>15 right?</p> <p>16 A. Correct.</p> <p>17 Q. -- depletion is required for</p> <p>18 protein binding to occur after APAP.</p> <p>19 Dose-response data supporting this were first</p> <p>20 published 40 years ago.</p> <p>21 And then you go on to say:</p> <p>22 However, more recent work has challenged this</p> <p>23 idea. Protein adducts could be measured in</p> <p>24 human HepaRG cells as early as one hour after</p> <p>25 treatment with APAP, well before any</p>
<p style="text-align: right;">Page 143</p> <p>1 N-acetyl-p-benzoquinone imine, NAPQI.</p> <p>2 It is now thought that binding</p> <p>3 to proteins, mitochondrial proteins in</p> <p>4 particular, causes oxidative stress and</p> <p>5 mitochondrial damage resulting in necrotic</p> <p>6 cell death.</p> <p>7 You wrote that, right?</p> <p>8 A. Yes. This is what we call, as</p> <p>9 I mentioned previously when we were</p> <p>10 discussing my methodology and how I weigh or</p> <p>11 compare studies, this is -- protein binding</p> <p>12 is an event that we would consider in science</p> <p>13 necessary but not sufficient.</p> <p>14 You can have protein binding</p> <p>15 without toxicity. So in other words, you</p> <p>16 have to have protein binding to get toxicity</p> <p>17 in the liver, and -- but it's not enough.</p> <p>18 It's not enough just to have some protein</p> <p>19 adducts.</p> <p>20 Q. And if we go to page 5.</p> <p>21 Mechanisms of the appearance of APAP-protein</p> <p>22 adducts in plasma, you wrote: We have</p> <p>23 hypothesized that the appearance of</p> <p>24 APAP-protein adducts in plasma occurs in one</p> <p>25 of two ways. Protein binding may take place</p>	<p style="text-align: right;">Page 145</p> <p>1 appreciable loss of glutathione had occurred.</p> <p>2 And you cite to yourself from</p> <p>3 2011, right?</p> <p>4 A. Yes.</p> <p>5 Q. Moreover, protein-derived</p> <p>6 APAP-CYS could be detected in serum from</p> <p>7 humans after only therapeutic doses, citing</p> <p>8 to Heard 2011.</p> <p>9 Do you see that?</p> <p>10 A. Yes.</p> <p>11 Q. Where in your report did you</p> <p>12 address that protein-derived APAP-CYS could</p> <p>13 be detected in humans from only therapeutic</p> <p>14 doses?</p> <p>15 A. So it wasn't really relevant to</p> <p>16 my report for the reason being that it's most</p> <p>17 likely -- since the liver is the primary site</p> <p>18 of drug metabolism, it's most likely that all</p> <p>19 circulating acetaminophen-protein adducts</p> <p>20 come from the liver. There's no reason to</p> <p>21 believe it comes from the brain at all.</p> <p>22 So this observation is not</p> <p>23 really relevant to what we're talking about.</p> <p>24 And again, protein binding is necessary but</p> <p>25 not sufficient for toxicity.</p>

<p>Page 146</p> <p>1 Q. Protein binding is what?</p> <p>2 A. Necessary but not sufficient</p> <p>3 for toxicity. So seeing protein binding is</p> <p>4 not an indication of toxicity. It's a</p> <p>5 necessary thing; you have to see it in the</p> <p>6 liver after overdose, and that's what the</p> <p>7 plaintiffs opine would happen in the brain as</p> <p>8 well. So it's a necessary thing. But just</p> <p>9 having some doesn't mean you get toxicity.</p> <p>10 And again, yeah, these are</p> <p>11 probably mostly coming from the liver since</p> <p>12 that is the major site of drug metabolism,</p> <p>13 including acetaminophen metabolism.</p> <p>14 Q. And when you say for toxicity,</p> <p>15 you can only speak to for liver toxicity,</p> <p>16 right?</p> <p>17 A. So when I say toxicity,</p> <p>18 toxicity occurs with -- is known --</p> <p>19 established to occur with acetaminophen</p> <p>20 overdose in the liver and in some patients in</p> <p>21 the kidney. So that's what most of our</p> <p>22 statements and research have focused on.</p> <p>23 Q. You're aware, though, of</p> <p>24 protein binding occurring in other tissue</p> <p>25 matter, right?</p>	<p>Page 148</p> <p>1 Importantly, we were able to</p> <p>2 detect protein binding after treatment with</p> <p>3 15 milligrams per kilogram APAP at these</p> <p>4 earlier time points, with only a minimal loss</p> <p>5 of liver GSH. Together, it is clear from</p> <p>6 these studies that some protein binding can</p> <p>7 occur without extensive GSH depletion and</p> <p>8 without toxicity.</p> <p>9 Do you see that?</p> <p>10 A. I see that. I would also like</p> <p>11 to note "minimal" is a relative term, right?</p> <p>12 At the other doses, we also see almost</p> <p>13 complete glutathione depletion. At the</p> <p>14 15-milligram per kilogram dose, if you look</p> <p>15 at panel A of Figure 2, there was still loss</p> <p>16 of glutathione, as I said before.</p> <p>17 Q. What did you do -- let me ask</p> <p>18 you something.</p> <p>19 Do you believe that the</p> <p>20 question of babies in utero being protected</p> <p>21 from a potential harmful toxic product is a</p> <p>22 serious concern?</p> <p>23 MR. COHEN: Object to the form.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. In other words, to study that,</p>
<p>Page 147</p> <p>1 A. We have provided a little bit</p> <p>2 of data that there might be some in the lung.</p> <p>3 Q. I'm not talking about you</p> <p>4 personally, your studies.</p> <p>5 A. Right.</p> <p>6 Q. You are personally aware as a</p> <p>7 scientist that protein adduct binding occurs</p> <p>8 in the brain, right?</p> <p>9 A. Absolutely not. No, no. There</p> <p>10 are no acetaminophen-protein adducts detected</p> <p>11 in the brain by anyone who's attempted to</p> <p>12 measure it, even after massive overdoses of</p> <p>13 acetaminophen.</p> <p>14 Q. We're going to go through the</p> <p>15 brain a little more later on and address your</p> <p>16 brain studies to address the relevancy of</p> <p>17 what you have set forth in your expert</p> <p>18 report.</p> <p>19 And then further on here at</p> <p>20 page 7: Our results show that the peak of</p> <p>21 protein adduct formation in the liver is</p> <p>22 reached by half hour -- a half to one hour</p> <p>23 after administration of subtoxic doses and</p> <p>24 that adduct concentration decreases</p> <p>25 thereafter.</p>	<p>Page 149</p> <p>1 it's important to study it because it's a --</p> <p>2 it's an in utero baby that we're talking</p> <p>3 about, right?</p> <p>4 MR. COHEN: Same objection.</p> <p>5 A. It's important to -- it would</p> <p>6 be -- if you're concerned that in utero</p> <p>7 exposure to some chemical might have adverse</p> <p>8 effects on the offspring, that's an important</p> <p>9 concern and it's worth studying.</p> <p>10 BY MR. JANUSH:</p> <p>11 Q. From a perspective of</p> <p>12 methodology, what did you do in this case,</p> <p>13 when considering that Tylenol is a drug that</p> <p>14 can be taken repeatedly at therapeutic doses</p> <p>15 over consecutive days by a pregnant woman, to</p> <p>16 determine what the impact of that minimal</p> <p>17 protein binding that you spoke of earlier</p> <p>18 would be over time when glutathione is not</p> <p>19 being completely depleted?</p> <p>20 MR. COHEN: Object to form.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. What did you do to rule in or</p> <p>23 rule out what the impact of that concern is?</p> <p>24 A. Well, that's not what I was</p> <p>25 asked to address, right. I mean, these</p>

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1 clinical outcomes, it's not -- I'm not an
 2 epidemiologist. I'm -- I'm not a physician.
 3 I wasn't asked to address --
 4 Q. I'm not talking about the
 5 epidemiology. I'm talking about causation.
 6 I'm talking about the fact that you are a
 7 scientist that studies primarily, from all
 8 your publications that I've seen and from
 9 what you acknowledge today, liver toxicity,
 10 and primarily within the field of liver
 11 toxicity, single-dose overdose analysis.
 12 So I'm asking: In a case like
 13 this, where we are undoubtedly not addressing
 14 single-dose overdoses of Tylenol but, rather,
 15 cumulative doses, what did you do to satisfy
 16 your safety concern for babies that -- and
 17 ensure that your opinion is valid for the
 18 women, the pregnant mother who's taking
 19 Tylenol repeatedly, day after day during her
 20 pregnancy?
 21 What did you do to eliminate a
 22 concern that protein binding with minimal
 23 loss of liver GSH wouldn't be harmful to a
 24 baby?
 25 MR. COHEN: Object to form.

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1 Go ahead.
 2 A. That's a very long question.
 3 First of all --
 4 BY MR. JANUSH:
 5 Q. It is, and I can break it down,
 6 but I'm trying to tell a story with
 7 you because --
 8 A. I'm prepared to answer the
 9 question.
 10 Q. Okay. Good.
 11 A. So, first of all, it's a bit
 12 strange to me that you're sort of harping on
 13 the single-dose overdose when your own
 14 plaintiffs' experts relied extensively on
 15 data from studies that use single doses.
 16 In addition to that, when
 17 you're talking about, you know, what did I
 18 do, well -- to assuage my concern that there
 19 might be an effect on the child, well, first
 20 of all, there are no data on
 21 acetaminophen-protein binding in the fetal
 22 brain after maternal ingestion of therapeutic
 23 doses of acetaminophen.
 24 The only data that we have on
 25 acetaminophen-protein binding in the brain

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1 comes from rodent studies where they gave
 2 massive overdoses of acetaminophen and failed
 3 to detect any evidence of protein binding.
 4 So if massive overdoses don't
 5 cause NAPQI formation in the brain, I'm not
 6 too worried about it at therapeutic
 7 overdoses.
 8 Q. And we're going to get to what
 9 you consider massive overdoses.
 10 MR. COHEN: If you're at a
 11 convenient spot, we've been going over
 12 an hour again. Can we take a break?
 13 MR. JANUSH: Sure.
 14 MR. COHEN: Thanks.
 15 THE VIDEOGRAPHER: We are going
 16 off record. The time is 11:26.
 17 (Recess taken, 11:26 a.m. to
 18 12:25 p.m. CDT)
 19 THE VIDEOGRAPHER: We are going
 20 back on record. Time is 12:25.
 21 BY MR. JANUSH:
 22 Q. Dr. McGill, earlier before we
 23 broke for lunch, we had talked a bit about
 24 the paper you wrote with Stefanie
 25 Kennon-McGill. That's your wife, right?

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1 A. She's my wife and colleague.
 2 Q. Okay. So that, we're marking
 3 Extrahepatic toxicity of acetaminophen
 4 critical evaluation of the evidence and
 5 proposed mechanisms, by Kennon-McGill et al.
 6 as Plaintiffs' Exhibit 839 and handing it to
 7 you.
 8 (Whereupon, Deposition
 9 Exhibit P839, Extrahepatic toxicity of
 10 acetaminophen: critical evaluation of
 11 the evidence and proposed mechanisms,
 12 by Kennon-McGill et al., was marked
 13 for identification.)
 14 BY MR. JANUSH:
 15 Q. And this is from the Journal of
 16 Clinical and Translational Research,
 17 Extrahepatic toxicity of acetaminophen:
 18 critical evaluation of the evidence and
 19 proposed mechanisms.
 20 This is the review paper that
 21 you did, right? This isn't original science;
 22 it's just original summary of literature from
 23 your perspective, right?
 24 A. Just a point of clarity. You
 25 referred to it as the review paper. I've

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1 written more than one review but --

2 Q. The one we discussed though.

3 A. The one we discussed earlier,

4 it is that paper.

5 With regard to the question of

6 it does not represent original experimental

7 research, but again, when you write a review

8 like this, you try to critically evaluate the

9 data in the literature, so it's still a

10 critical analysis.

11 Q. And this was published in 2017;

12 is that correct?

13 A. That's correct. That's what it

14 lists on the article info.

15 Q. Okay.

16 A. It came -- yeah, that's fine.

17 Q. And right now, we're going to

18 focus on, for the moment, the abstract where

19 it says "relevance for patients."

20 Do you see that?

21 A. Yes.

22 Q. And on the third line down, it

23 says: Recent studies have suggested that

24 APAP can damage cells in other organs as

25 well.

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1 How can APAP damage cells in

2 other organs as well?

3 A. So to be clear, what we're

4 saying there is just pointing out that there

5 has -- concerns have been raised about this

6 possibility, so we're not promoting that

7 statement, which is why we used the word

8 "suggested."

9 Now, in terms of how it can

10 promote -- how it could promote toxicity in

11 other organs, while the --

12 Q. Let me actually make it easier.

13 What other organs are we

14 talking about that APAP can -- that it has

15 been suggested that APAP can damage cells

16 within?

17 MR. COHEN: Object to the form.

18 He was interrupted.

19 Go ahead.

20 A. So what we discuss here in the

21 paper -- we can go through it section by

22 section, if you'd like. You can -- Section 2

23 is about -- is background essentially.

24 Section 3 is about nephrotoxicity, so this

25 is -- we're looking -- addressing the issue

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1 of toxicity in the kidney. Section 4 is

2 about pulmonary toxicity. There have been

3 claims that there may be some pulmonary

4 toxicity of acetaminophen, at least -- and so

5 we tried to address that here.

6 There have been claims

7 regarding endocrine disruption and sexual

8 effects on -- excuse me, effects on -- well,

9 effects on the endocrine system and sexual

10 development. There have been claims of

11 ototoxicity, so that's hearing loss, damage

12 in the ear.

13 And then we finally

14 addressed -- well, not finally, but claims of

15 neurodevelopmental, neurobehavioral

16 disorders.

17 BY MR. JANUSH:

18 Q. So earlier when we spoke, early

19 on in this deposition you addressed that you

20 aren't the expert on neurodevelopmental

21 disorders, right?

22 A. I am not an expert on

23 neurodevelopmental disorders, correct.

24 Q. And you also discussed that you

25 are not an expert on epidemiology, correct?

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1 A. I'm not an epidemiologist,

2 correct.

3 Q. What led you to undertake a

4 scientific review to address

5 neurodevelopmental and neurobehavioral

6 disorders and assess literature and weigh in

7 on this topic as someone who's admittedly not

8 an expert in this field?

9 A. Right. A couple of things.

10 So, first of all, this is not -- this paper

11 is not a review of the neurodevelopmental

12 claims; this section of the paper is. Just a

13 point of clarity.

14 The other issue -- another

15 issue is, actually, my wife is a

16 neuroscientist, and she actually did her

17 postdoctoral research on autism spectrum

18 disorders, and we wrote this together.

19 And in addition to that, in

20 terms of some of the other aspects, such as

21 epidemiological studies, we were careful to

22 cite -- you know, when some of these

23 epidemiological claims came out, there were a

24 number of letters to the editor and editorial

25 comments published in the same journals or

<p style="text-align: right;">Page 158</p> <p>1 some different journals by people who have 2 greater expertise and experience in 3 epidemiology than I, and we've cited some of 4 those documents for those specific concerns 5 that we've listed. And so I'm kind of 6 channeling those experts. 7 Q. So did your wife take the 8 laboring oar on the topic concerning 9 Section 7, Neurodevelopmental and 10 neurobehavioral disorders, when drafting this 11 piece of literature? 12 A. I'm sorry, I'm not familiar 13 with the term -- what was it? The "laboring 14 oar"? 15 Q. In other words, did your wife 16 carry the water, do the majority of the 17 writing and research regarding 18 neurodevelopmental and neurobehavioral 19 disorders when addressing Section 7 of this 20 journal? 21 A. I don't remember the exact 22 proportion of who wrote what. I mean, 23 there's some material in here about sulfation 24 and -- and glucuronidation. 25 THE WITNESS: Sorry about that,</p>	<p style="text-align: right;">Page 160</p> <p>1 miscarriage that has been reported in a few 2 studies. As a result, most pregnant women 3 rely on APAP to control fever and pain. If 4 it can be shown that APAP also poses a 5 significant risk of congenital abnormalities, 6 then that may result in removal of the only 7 remaining treatment option for those 8 patients. 9 Did I read that correctly? 10 A. Yes, you read it correctly. 11 Q. Did either you -- were you or 12 your wife, or collectively both of you, 13 concerned that if acetaminophen could be 14 shown to be related to specific 15 neurodevelopmental disorders such as ASD or 16 ADD or ADHD, that Tylenol could -- could be 17 removed as an option for pregnant women? 18 MR. COHEN: Objection, form. 19 A. I'm sorry, it's kind of a long 20 question. Would you mind -- 21 BY MR. JANUSH: 22 Q. Were you concerned, in writing 23 this review and researching Tylenol and 24 acetaminophen and its potential impacts on 25 pregnant women and their in utero babies,</p>
<p style="text-align: right;">Page 159</p> <p>1 I'll try to keep that in mind. 2 A. So questions of acetaminophen 3 metabolism, and so I most likely wrote that. 4 With regard to some of the other materials, 5 she most likely contributed a great deal. 6 But again, this is -- we wrote 7 this in 2017, six years ago, so I don't 8 recall the exact proportions. 9 BY MR. JANUSH: 10 Q. Okay. And at the last sentence 11 on the first page of the abstract it says: 12 It is especially important to view claims of 13 developmental effects of antenatal APAP 14 exposure with a critical eye because APAP is 15 currently the only over the counter 16 medication recommended for pregnant women to 17 self-treat pain and fever. 18 Did I read that correctly? 19 A. Yes, you read it correctly. 20 Q. And if we flip to the very last 21 page, and we'll start at the top of the 22 left-hand column, its -- it reads, on the 23 fourth line down: Typically, pregnant women 24 are advised not to use NSAIDs due to the 25 increased risk of birth defects and</p>	<p style="text-align: right;">Page 161</p> <p>1 that if scientists who are claiming that ADD 2 and ADHD is caused by the drug, that this 3 drug wouldn't be available to pregnant women? 4 MR. COHEN: Objection, form. 5 A. I'm not entirely sure I 6 understand. I think I understand what you're 7 asking. 8 BY MR. JANUSH: 9 Q. In other words -- 10 A. So -- 11 Q. Let me phrase it differently. 12 Why -- why were -- wasn't your 13 primary concern the question of protecting 14 the fetus as opposed to what drug is 15 available to treat a -- to treat pain? 16 A. I mean, this is a very broad -- 17 you're getting into issues of ethics and that 18 sort of thing. I don't know that I would say 19 it was -- I mean, there are two issues to 20 consider here, right, the benefit of the 21 mother, which there's a clear benefit to the 22 mother for using acetaminophen, right? 23 Again, the -- it's the only 24 drug available -- generally speaking, the 25 only drug recommended for pregnant women to</p>

<p style="text-align: right;">Page 162</p> <p>1 use to control pain and fever. So there's a 2 clear, well-established, significant benefit. 3 If you balance that with the 4 risk of the -- any potential harm to the 5 fetus, well, then you'd better have very good 6 data to justify removing that treatment, the 7 last treatment for the mother. 8 And our summary here, our 9 analysis of these literature was just that 10 you don't have very good data in support of 11 that concern. 12 Q. And this is 2017. What did you 13 do, if anything, since 2017? Did you and 14 your wife endeavor to research all of the 15 literature that has developed since then 16 before being retained as an expert since this 17 subject had interested you? 18 A. So in the intervening years, 19 I've maintained what I would say is a passing 20 interest in the topic. I've tried to stay up 21 on some of the literature, but not in great 22 detail, other than what I've been asked to 23 address in this case. 24 The reason for that, if you 25 care to know, is -- right, we're just busy</p>	<p style="text-align: right;">Page 164</p> <p>1 acetaminophen? 2 A. This is a section that's 3 required by this particular journal, and so 4 yes, they ask you to comment on things that 5 might be relevant for patients. That's why 6 it says Relevance for Patients. 7 Q. So to summarize, let's talk 8 about some of the tissues in the body that 9 acetaminophen affects that you've addressed 10 in this journal publication. 11 You agree it affects the liver, 12 right? 13 MR. COHEN: Object to form. 14 A. Well, I agree that overdose 15 causes liver injury. 16 BY MR. JANUSH: 17 Q. You agree that acetaminophen 18 affects kidneys, right? 19 MR. COHEN: Object to form. 20 A. Acetaminophen overdose causes 21 kidney injury in some patients. 22 BY MR. JANUSH: 23 Q. You agree that acetaminophen 24 affects lungs, right? 25 MR. COHEN: Object to form.</p>
<p style="text-align: right;">Page 163</p> <p>1 with other projects, funded projects, and 2 things that are funded by a sponsor take 3 priority because we have to complete those to 4 satisfy the sponsor. 5 Q. And because it's not your 6 primary area of study interest for which you 7 are sponsored, right? 8 A. We don't have any grants or 9 funding specifically for this topic. 10 Q. Did you ever apply for grants 11 or funding specifically for this topic? 12 A. I have not yet. 13 Q. Are you going to? 14 A. I can't say for sure. Yeah. 15 Q. And I'm going to have Michael 16 search for me for a section called Relevance 17 for Patients. 18 A. I -- I believe that's in the 19 abstract. 20 Q. Oh, there it is. Yes. Okay. 21 So we were addressing that earlier. 22 A. Yes. 23 Q. Is this section devoted to 24 information that might be clinically relevant 25 for people taking or recommending</p>	<p style="text-align: right;">Page 165</p> <p>1 A. It's quite a bit more 2 controversial. I'd say it's not well 3 established. There's no evidence of overt 4 lung toxicity. Some concerns have been 5 raised by other people. 6 BY MR. JANUSH: 7 Q. And you agree, including you've 8 published on it, that acetaminophen -- well, 9 you agree that acetaminophen can affect the 10 ears as well, right? 11 MR. COHEN: Object to form. 12 A. No. Well, we -- the conclusion 13 from that -- our conclusion from the data 14 that we obtained from that study and from 15 some related studies was that there is no 16 ototoxicity, even with large overdoses. 17 BY MR. JANUSH: 18 Q. But you found -- I'll move on 19 to the next question. 20 Dr. McGill, in this paper you 21 say that no mechanistic studies had been 22 performed on the relationship between 23 acetaminophen and neurodevelopment, right? 24 A. I -- 25 MR. COHEN: Object to form.</p>

<p style="text-align: right;">Page 166</p> <p>1 A. Can you point me to where --</p> <p>2 MR. COHEN: Yeah, go ahead.</p> <p>3 A. Can you point me to where I</p> <p>4 state that?</p> <p>5 BY MR. JANUSH:</p> <p>6 Q. Yeah, it's in the section on</p> <p>7 neurodevelopmental disorders.</p> <p>8 No mechanistic -- last page,</p> <p>9 Biological relevance and future studies.</p> <p>10 Third line of the last paragraph on the</p> <p>11 left-hand side: No mechanistic studies have</p> <p>12 been performed, and the few mechanisms that</p> <p>13 have been proposed have not been directly</p> <p>14 tested.</p> <p>15 A. That's the statement that I</p> <p>16 made at the time that we wrote this.</p> <p>17 Q. At that time, how did you come</p> <p>18 to that conclusion? Did you perform a</p> <p>19 literature search?</p> <p>20 A. Yes.</p> <p>21 Q. And were you unaware of the</p> <p>22 Viberg paper that was done in 2014?</p> <p>23 A. I can't say what I was aware of</p> <p>24 or not aware of at that time.</p> <p>25 Q. But you apparently didn't find</p>	<p style="text-align: right;">Page 168</p> <p>1 and ADD/ADHD-like behavior in mice and found</p> <p>2 no evidence to support it.</p> <p>3 And I believe, if I can have a</p> <p>4 moment to look through it again...</p> <p>5 (Document review.)</p> <p>6 A. I mean -- so understanding that</p> <p>7 we wrote this, yeah, six years ago at least,</p> <p>8 and -- and I haven't had time to review the</p> <p>9 entire document, I guess I was referring to</p> <p>10 that study that I just mentioned where I</p> <p>11 quoted from.</p> <p>12 BY MR. JANUSH:</p> <p>13 Q. Did you do a Bradford Hill</p> <p>14 analysis when addressing the, quote,</p> <p>15 conflicting, quote, epidemiological studies</p> <p>16 you referred to in this journal review?</p> <p>17 A. Again, so I'm not an</p> <p>18 epidemiologist, and doing -- using the</p> <p>19 Bradford Hill criteria is not standard in</p> <p>20 my -- in my area of research.</p> <p>21 What we did do, again, as I</p> <p>22 stated earlier, is cited experts, people who</p> <p>23 have more expertise in patient care or</p> <p>24 epidemiology than I, and just to describe</p> <p>25 some of the concerns that they have raised.</p>
<p style="text-align: right;">Page 167</p> <p>1 it in your literature search, right?</p> <p>2 A. I don't know. You'd have to --</p> <p>3 I may have found it and deemed it irrelevant.</p> <p>4 I don't know. I'd have to see the paper, and</p> <p>5 even if I saw the paper, I don't know what I</p> <p>6 was thinking six years ago or seven years ago</p> <p>7 when we actually wrote it.</p> <p>8 Q. When you addressed that</p> <p>9 conflicting epidemiological studies exist,</p> <p>10 what conflicting epidemiological studies were</p> <p>11 you referring to in this paragraph?</p> <p>12 A. So I'll tread carefully here</p> <p>13 because, again, I'm not an epidemiologist,</p> <p>14 but for -- if you'll just give me a moment.</p> <p>15 (Document review.)</p> <p>16 A. So, for example, on the prior</p> <p>17 page, 303, the right column near the bottom,</p> <p>18 we stated here -- this is with -- I think</p> <p>19 this section is -- I haven't had a chance to</p> <p>20 reread it all in detail. I think in the</p> <p>21 section we're referring to ADHD, and we just</p> <p>22 noted that it seemed like there was at least</p> <p>23 one study -- so we say -- state specifically:</p> <p>24 Interestingly, one group has even tested the</p> <p>25 association between prenatal acetaminophen</p>	<p style="text-align: right;">Page 169</p> <p>1 Q. But just to even write a</p> <p>2 statement like: No mechanistic studies have</p> <p>3 been performed, and the few mechanisms that</p> <p>4 have been proposed have not been directly</p> <p>5 tested. In fact, there is strong evidence</p> <p>6 that ASD, in particular, is driven by</p> <p>7 genetics, so exposure to APAP or other</p> <p>8 xenobiotics may not be important.</p> <p>9 And then you get into: Males</p> <p>10 are more likely to develop ASD, and siblings</p> <p>11 of children with ASD are at greater risk,</p> <p>12 period.</p> <p>13 And so these are weighty</p> <p>14 scientific conclusions that you are drawing</p> <p>15 as someone who's not an epidemiologist. How</p> <p>16 did you feel qualified to even write this</p> <p>17 piece of literature here at that paragraph at</p> <p>18 Section 7?</p> <p>19 MR. COHEN: Objection, form.</p> <p>20 A. As I stated earlier, with</p> <p>21 regard to ASD, my wife is a neuroscientist</p> <p>22 and did her postdoctoral research in ASD. So</p> <p>23 this was -- as I recall, this was one of her</p> <p>24 contributions, particularly the genetic --</p> <p>25 the role of genetics and so on.</p>

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1 Again, other people with
 2 expertise in epidemiology, I mean, as you've
 3 seen, other defense expert reports have
 4 raised significant concerns about biases and
 5 confounding in the epidemiological studies.
 6 The best I can do is channel
 7 their opinions when it comes to epidemiology,
 8 and so that's what we did with the opinions
 9 that we saw at the time.
 10 BY MR. JANUSH:
 11 Q. Okay. I'm going to go back to
 12 your report. We're going to turn to
 13 page 19 -- sorry, page 9, paragraph 19, where
 14 I'm addressing your language, quote: It is
 15 critical that any experimental model of
 16 therapeutic acetaminophen exposure mimics
 17 these concentrations and durations. And
 18 you're speaking about concentrations you
 19 addressed in paragraph 18.
 20 A. Uh-huh.
 21 Q. A model that results in
 22 substantially higher concentrations or
 23 exposure to acetaminophen for inappropriate
 24 lengths of time cannot be said to model
 25 therapeutic use in humans.

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1 And here's where I'd like to
 2 focus the next two sentences: Although it is
 3 tempting to refer to any sub-hepatotoxic dose
 4 or concentration of acetaminophen as
 5 therapeutic, that is incorrect. The terms
 6 "therapeutic" and "sub-hepatotoxic" are not
 7 interchangeable.
 8 You wrote that, right?
 9 A. Yes.
 10 Q. Do you believe in that today
 11 still?
 12 A. Absolutely.
 13 Q. Okay. You go on to address
 14 rats and how they're highly resistant to the
 15 hepatotoxic effects of acetaminophen, right?
 16 A. Yes. I also -- sorry.
 17 Q. First I want to address your
 18 statement that the terms "therapeutic" and
 19 "sub-hepatotoxic" are not interchangeable.
 20 That's wrong, isn't it?
 21 A. Absolutely not.
 22 Q. Have you stated the opposite in
 23 published literature?
 24 A. No.
 25 Q. No? Okay.

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1 Do you remember publishing an
 2 article with Hu and Jaeschke called Low-dose
 3 Acetaminophen Induces Reversible
 4 Mitochondrial Dysfunction Associated with
 5 Transient c-Jun N-terminal Kinase Activation
 6 in Mouse Liver in 2016?
 7 A. Sure do.
 8 Q. Okay. We've marked that as
 9 P837.
 10 (Whereupon, Deposition
 11 Exhibit P837, Low-Dose Acetaminophen
 12 Induces Reversible Mitochondrial
 13 Dysfunction associated with Transient
 14 c-Jun N-Terminal Kinase Activation in
 15 Mouse Liver, by Hu et al., was marked
 16 for identification.)
 17 BY MR. JANUSH:
 18 Q. Let's go -- first page, 204,
 19 bottom of the left side under the bold black
 20 line: APAP toxicity shows a threshold
 21 dose-dependence such that therapeutic doses
 22 are generally considered nontoxic.
 23 Did I read that correctly?
 24 A. Yes.
 25 Q. That's the exact opposite of

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1 what you wrote at paragraph 19, page 9, isn't
 2 it?
 3 A. No.
 4 Q. Well, let's look at
 5 paragraph 18, page 9 -- paragraph 19 again.
 6 The terms "therapeutic" and "sub-hepatotoxic"
 7 are not interchangeable.
 8 Sub-hepatotoxic means nontoxic,
 9 right?
 10 A. No, it does not.
 11 Q. It's below the -- it's --
 12 sub-hepatotoxic is below the level of
 13 toxicity.
 14 A. No, no, no. We are not -- this
 15 statement cannot be reversed. That's kind of
 16 what you're doing. You're saying -- let me
 17 rephrase this.
 18 The statement that a
 19 therapeutic dose is nontoxic is a truism,
 20 essentially. Of course a therapeutic dose is
 21 not toxic, right? That does not mean that
 22 all nontoxic doses are therapeutic.
 23 Q. Your statement in the
 24 paragraph 19: Although it is tempting to
 25 refer to any sub-hepatotoxic dose or

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1 concentration of acetaminophen as
 2 therapeutic, that is incorrect.
 3 You wrote that, right?
 4 A. Yes, I did.
 5 Q. And here you're writing: APAP
 6 toxicity shows a threshold dose-dependence
 7 such that therapeutic doses are generally
 8 considered nontoxic.
 9 A. Yes. Once again --
 10 Q. So you're saying that doesn't
 11 go in the reverse direction?
 12 A. Absolutely not, no.
 13 MR. COHEN: I think that was a
 14 double negative.
 15 A. You're saying that doesn't
 16 go -- you're saying -- I'm sorry. Let me
 17 reconsider that. Maybe I made a mistake.
 18 You're saying that -- you're
 19 saying that it doesn't go in the reverse
 20 direction. I'm sorry.
 21 Yes, I'm saying that doesn't go
 22 in the reverse direction. I apologize. I'll
 23 try to slow down and consider it a bit more.
 24 BY MR. JANUSH:
 25 Q. So let me -- let me say this.

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1 Dr. McGill, I'm going to use
 2 this paper to make the point that nontoxic
 3 doses of acetaminophen that do not cause
 4 transaminase release and histological
 5 necrosis, i.e., doses that would be
 6 overdoses, can nonetheless lead to transient
 7 hepatocellular mitochondrial dysfunction and
 8 steatosis, right?
 9 A. I don't know if that -- you're
 10 stating that that's what you're going to
 11 show.
 12 Q. That's what you wrote, right?
 13 A. I don't know if that's what
 14 you're going to show.
 15 Q. You wrote that though. These
 16 are your words.
 17 A. Sorry, you didn't tell me you
 18 were quoting anything in that question.
 19 Q. I purposely didn't because I
 20 wanted to see if you were going to fuss with
 21 me like you have been all day. You just
 22 fussed with me over your own words.
 23 MR. COHEN: Object to the form.
 24 BY MR. JANUSH:
 25 Q. So let's go to page 214.

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1 A. I'd like to state right away,
 2 what you said is not true. An overdose is
 3 really -- I mean, you can quarrel over what's
 4 a supertherapeutic dose, what's an overdose.
 5 An overdose is not just a dose that causes
 6 liver injury. An overdose is an excessive
 7 dose that's more than the therapeutic dose.
 8 Q. Okay. Let's go to your
 9 conclusion, page 214. In conclusion, this
 10 study shows that even nontoxic doses of APAP
 11 that do not cause transaminase release and
 12 histological necrosis can nonetheless lead to
 13 transient hepatocellular mitochondrial
 14 dysfunction and steatosis.
 15 Did I read that right?
 16 A. Yes.
 17 Q. Is oxidative stress associated
 18 with mitochondrial dysfunction?
 19 A. In the case of acetaminophen
 20 overdose in the liver, oxidative stress is
 21 associated with mitochondrial dysfunction.
 22 Q. Okay. And here, you're not
 23 addressing acetaminophen overdose. You're
 24 addressing a nontoxic dose that can
 25 nonetheless lead to mitochondrial

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1 dysfunction, aren't you?
 2 A. No. This paper only looked at
 3 overdoses. The lowest dose we used was
 4 75 milligrams per kilogram. A normal dose --
 5 I'm sorry, may I please finish the question?
 6 Q. I didn't interrupt you.
 7 A. May I please finish the answer?
 8 Q. I didn't interrupt you. I was
 9 silent.
 10 A. So a normal dose in a human is
 11 one gram at one time. An average body weight
 12 for a person is 70 kilograms, although I'm
 13 not sure that applies to me. And so if you
 14 do that calculation, so that's 1,000
 15 milligrams, right, one gram. Divided by
 16 70 kilograms, you get about 14 milligrams per
 17 kilogram. That is far lower than
 18 75 milligrams per kilogram.
 19 Furthermore, the effects of
 20 transient mitochondrial dysfunction and
 21 steatosis were not observed at that lowest
 22 dose that we use, that lowest overdose,
 23 75 milligram per kilogram.
 24 And finally, the operative word
 25 here is "transient." The point of this

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1 paper, from my point of view as a scientist
 2 involved in this study, my interest in this
 3 was that at the time it was thought, by some
 4 people, anyway, that mitochondrial
 5 depolarization was an irreversible step in
 6 cell death, and that once that occurred, the
 7 cells would die. This paper demonstrated
 8 that that's not the case. So it was a
 9 transient effect from which the cells
 10 recovered quickly.

11 So again, these are still
 12 overdoses. Even the lowest overdose showed
 13 no effect, and even the effects that were
 14 observed at the higher dose was a transient
 15 effect and the cells recovered.

16 Q. So, first of all, just to be
 17 clear, we're talking about the liver again,
 18 right?

19 A. Yes.

20 Q. Okay.

21 A. Liver and overdose.

22 Q. And second of all -- I'm
 23 looking at your conclusion. Are we reading
 24 the same sentence: In conclusion, this study
 25 shows that even nontoxic, quote -- you quoted

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1 it, not me -- doses of APAP that do not cause
 2 transaminase release and histological
 3 necrosis can nonetheless lead to transient
 4 hepatocellular mitochondrial dysfunction and
 5 steatosis.

6 You said that, not me, right?

7 A. That's what we wrote in the
 8 paper. Nontoxic does not mean therapeutic.

9 Q. It also doesn't mean overdose.

10 MR. COHEN: Object to the form.

11 BY MR. JANUSH:

12 Q. Right?

13 A. Overdoses can be not overtly
 14 toxic.

15 Q. So is it your testimony in this
 16 case that you intended, when using nontoxic,
 17 no quotes, doses of APAP, to mean it's
 18 actually an overdose dose but it is not
 19 toxic?

20 MR. COHEN: Objection, form.

21 A. I mean, essentially, yes.

22 It's -- it is still an overdose. It just
 23 didn't cause overt liver injury based on
 24 transaminase release and histology.

25 ///

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1 BY MR. JANUSH:

2 Q. Here's where I'm stuck, and I'm
 3 going to have to ask you to help me get
 4 unstuck. Because after the exact sentence I
 5 read, you then use the words "Unlike
 6 overdose-induced hepatotoxicity, the effects
 7 of subtoxic APAP are comparably mild and
 8 reversible and correlate with JNK activation
 9 and mitochondrial translocation.

10 You wrote that, right?

11 A. That's what we collectively
 12 stated in the article.

13 Q. So you're addressing that this
 14 isn't -- this is unlike an overdose --

15 A. No, no. I said it's unlike
 16 overdose-induced hepatotoxicity.

17 Q. Right.

18 A. A critical point.

19 Q. Unlike overdose-induced
 20 hepatotoxicity. And then later you say:
 21 However, in patients subjected to other
 22 stresses, APAP-induced transient
 23 mitochondrial dysfunction may lead to overt
 24 transaminase release and necrosis.

25 What other stresses were you

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1 speaking about?

2 A. At that time, there had been
 3 some concerns about, for example, patients
 4 with chronic liver diseases taking
 5 acetaminophen may be more susceptible to
 6 acetaminophen toxicity. However, that idea
 7 is widely discredited now, partly through my
 8 own research.

9 Q. I'm going to move on to
 10 paragraph 20, where you address --

11 A. So paragraph 20 in my report?

12 Q. Paragraph 20 of your report at
 13 page 10, where you address that Dr. Cabrera
 14 and Dr. Louie try to justify the use of very
 15 large doses or concentrations of
 16 acetaminophen in experimental models by
 17 referencing human equivalent dose (HED)
 18 estimates from the U.S. Food and Drug
 19 Administration. And you say: This approach
 20 is scientifically invalid.

21 Did I read that right?

22 A. Yes.

23 Q. Are you actually saying that
 24 the reverse cannot be done, that you cannot
 25 have an AED, an animal equivalent dose?

<p style="text-align: right;">Page 182</p> <p>1 A. What I'm stating here is that</p> <p>2 the FDA guidance document -- I believe</p> <p>3 Dr. Louie tried to argue -- I can't recall if</p> <p>4 it was in his initial -- I believe --</p> <p>5 actually, Dr. Cabrera and Dr. Louie have both</p> <p>6 tried to rely on this FDA guidance as stating</p> <p>7 that going in the reverse direction from</p> <p>8 humans back to animals is an acceptable</p> <p>9 approach. The FDA guidance document never</p> <p>10 says that.</p> <p>11 Q. The reason the FDA guidance</p> <p>12 doesn't say that is because it was written in</p> <p>13 2005 with a purpose to protect</p> <p>14 first-in-human-use scenarios, right?</p> <p>15 A. That's correct.</p> <p>16 Q. It --</p> <p>17 A. Well --</p> <p>18 Q. Are you aware of the fact that</p> <p>19 even today, the FDA is considering</p> <p>20 potentially doing a preclinical trial?</p> <p>21 MR. COHEN: Object to form.</p> <p>22 BY MR. JANUSH:</p> <p>23 Q. A preclinical study.</p> <p>24 MR. COHEN: Object to form.</p> <p>25 A. I -- that's an incredibly broad</p>	<p style="text-align: right;">Page 184</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. Back to 839. Right above the</p> <p>3 numeral 8: Even a simple study could be</p> <p>4 performed in which pregnant mice -- now</p> <p>5 you're talking about mice, not women --</p> <p>6 receive 15 milligrams per kilograms APAP one</p> <p>7 to four times per day for several days, and</p> <p>8 behaviors associated with ASD and ADD/ADHD</p> <p>9 are measured in offspring over time.</p> <p>10 Here you're saying you could --</p> <p>11 there's no reason why you can't do an easy</p> <p>12 study with mice at low doses over time,</p> <p>13 right?</p> <p>14 A. Yes, which does not preclude</p> <p>15 doing it in humans.</p> <p>16 Q. You didn't address doing it in</p> <p>17 humans here, correct?</p> <p>18 A. I didn't say that you can't do</p> <p>19 that in humans.</p> <p>20 Q. I know. Now I'm going to ask</p> <p>21 you about the ethical implications.</p> <p>22 If you are testing for</p> <p>23 something as serious as ADHD and -- and</p> <p>24 autism spectrum disorder in offspring, why</p> <p>25 would you use women, pregnant women and their</p>
<p style="text-align: right;">Page 183</p> <p>1 question. I don't understand what you're</p> <p>2 asking me.</p> <p>3 BY MR. JANUSH:</p> <p>4 Q. So if the FDA wanted to test</p> <p>5 acetaminophen in utero, isn't the animal</p> <p>6 model the only way to ethically do that?</p> <p>7 A. If they -- again, this is a</p> <p>8 very broad question.</p> <p>9 Q. It's actually not a broad</p> <p>10 question.</p> <p>11 A. No, no. For its --</p> <p>12 Q. It's pretty narrow.</p> <p>13 MR. COHEN: Let him finish.</p> <p>14 A. Acetaminophen is currently an</p> <p>15 FDA-approved drug. There's no reason why you</p> <p>16 couldn't do a clinical trial in patients</p> <p>17 using therapeutic doses of acetaminophen in</p> <p>18 pregnant women.</p> <p>19 BY MR. JANUSH:</p> <p>20 Q. So -- so if, hypothetically --</p> <p>21 and by the way, just to be clear, in your</p> <p>22 review, you also conclude just that, right?</p> <p>23 You say -- the last page, right --</p> <p>24 MR. COHEN: Sorry, is this 839?</p> <p>25 ///</p>	<p style="text-align: right;">Page 185</p> <p>1 offspring, as potential guinea pigs?</p> <p>2 MR. COHEN: Object to the form.</p> <p>3 BY MR. JANUSH:</p> <p>4 Q. Wouldn't that be unethical?</p> <p>5 A. Listen, I'm not an ethicist.</p> <p>6 I'm not a philosopher. I can't opine on that</p> <p>7 question.</p> <p>8 Q. Do you know that your fellow</p> <p>9 experts for Johnson & Johnson say the exact</p> <p>10 opposite of you on this topic --</p> <p>11 MR. COHEN: Object --</p> <p>12 BY MR. JANUSH:</p> <p>13 Q. -- and just testified on this</p> <p>14 topic stating that they would never permit a</p> <p>15 patient of theirs to be enrolled in a</p> <p>16 clinical trial where the endpoint is to</p> <p>17 determine fetal safety?</p> <p>18 MR. COHEN: Object to the form.</p> <p>19 A. What I stated is that because</p> <p>20 it's an FDA-approved drug, I personally am</p> <p>21 unaware of any particular reason why you</p> <p>22 couldn't look at -- for example, you could do</p> <p>23 an observational study in women who choose to</p> <p>24 take acetaminophen of their own volition.</p> <p>25 So you're not administering it</p>

<p style="text-align: right;">Page 186</p> <p>1 to them; they're choosing to take it. And</p> <p>2 you could just observe the outcomes, which is</p> <p>3 effectively what's been done in the</p> <p>4 epidemiological studies -- well, anyway,</p> <p>5 certain ones.</p> <p>6 In addition to that, as I</p> <p>7 stated, I'm not an ethicist and I'm not going</p> <p>8 to comment on the ethics of any kind of study</p> <p>9 design.</p> <p>10 BY MR. JANUSH:</p> <p>11 Q. You understand, though, that</p> <p>12 the reason it's done retrospectively in</p> <p>13 epidemiological studies is specifically</p> <p>14 because you cannot test on pregnant women and</p> <p>15 their babies for injuries?</p> <p>16 MR. COHEN: Object to form.</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. Like what institutional review</p> <p>19 board would commit to passing this test?</p> <p>20 MR. COHEN: Object to form.</p> <p>21 A. Once again, I'm not an</p> <p>22 ethicist. I can't comment on the ethics of a</p> <p>23 trial like that. In addition, there are many</p> <p>24 reasons to do different kinds of studies.</p> <p>25 I'm sure there are more than one in the case</p>	<p style="text-align: right;">Page 188</p> <p>1 ask it differently.</p> <p>2 Do you appreciate the concept</p> <p>3 that a safe dose of Tylenol for an adult</p> <p>4 mother may be unsafe for a developing fetal</p> <p>5 brain?</p> <p>6 A. I'm aware of the concept of</p> <p>7 genetic susceptibility. I have not seen any</p> <p>8 data suggesting that what you've stated is</p> <p>9 correct.</p> <p>10 Q. Okay.</p> <p>11 A. Sorry, any reliable, rigorous,</p> <p>12 reproducible scientific data.</p> <p>13 Q. I'm not even going to address</p> <p>14 data. I'm just going to address logic and</p> <p>15 FDA guidance.</p> <p>16 As you sit here today, do you</p> <p>17 know whether infants, postnatal, should be</p> <p>18 given an adult dose of Tylenol?</p> <p>19 MR. COHEN: Object to the</p> <p>20 colloquy that preceded the question.</p> <p>21 Go ahead.</p> <p>22 BY MR. JANUSH:</p> <p>23 Q. Should infants be given an</p> <p>24 adult dose that's safe for an adult of</p> <p>25 Tylenol?</p>
<p style="text-align: right;">Page 187</p> <p>1 of epidemiological studies.</p> <p>2 BY MR. JANUSH:</p> <p>3 Q. Okay. You know, I have to go</p> <p>4 back before I go forward with the document</p> <p>5 that I had given you a moment ago. I forgot</p> <p>6 to deal with something with you.</p> <p>7 At paragraph 17, page 11 of</p> <p>8 your report, you address conversely all</p> <p>9 drugs --</p> <p>10 A. Sorry, page 11 doesn't have</p> <p>11 paragraph 17, so I want to make sure I'm</p> <p>12 looking in the right spot.</p> <p>13 Q. My apologies. I apologize.</p> <p>14 Page 8, Toxicology and Drug Safety.</p> <p>15 A. Uh-huh.</p> <p>16 Q. Paragraph 17 at the bottom of</p> <p>17 the page: Conversely, all drugs can be used</p> <p>18 safely at some dose.</p> <p>19 A. Yes, this is a fundamental</p> <p>20 tenet of toxicology.</p> <p>21 Q. Do you appreciate that what you</p> <p>22 just described as a fundamental tenet in</p> <p>23 toxicology is -- that there isn't necessarily</p> <p>24 a one size fits all, that all drugs can be</p> <p>25 used safely at some dose, meaning -- let me</p>	<p style="text-align: right;">Page 189</p> <p>1 A. So typically, when you dose,</p> <p>2 you don't just give -- well, first of all,</p> <p>3 I'm not a physician, certainly not a</p> <p>4 pediatrician. Can't really comment on what</p> <p>5 should or shouldn't be done.</p> <p>6 I'll just leave it at that.</p> <p>7 Q. Let me give you the dosing</p> <p>8 guide for Tylenol from Johnson & Johnson.</p> <p>9 We'll mark this as P836.</p> <p>10 (Whereupon, Deposition</p> <p>11 Exhibit P836, Dosing for Tylenol</p> <p>12 Children's & Infants' Medicine, was</p> <p>13 marked for identification.)</p> <p>14 BY MR. JANUSH:</p> <p>15 Q. If you look at the Infants Oral</p> <p>16 Suspension, acetaminophen, 160 milligrams per</p> <p>17 5 milliliters, weight less than 24 pounds,</p> <p>18 less than 2 years, ask a doctor.</p> <p>19 But when you're not a baby and</p> <p>20 you're two to three years old and you're not</p> <p>21 in utero, you're limited, if you weigh</p> <p>22 between 24 and 35 pounds, to 160 milligrams</p> <p>23 as your dose per 4 hours.</p> <p>24 160 milligrams per dose is by</p> <p>25 no means the adult dose for Tylenol, right?</p>

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1 A. I haven't done the math for
 2 this. I couldn't say. And in any case --
 3 Q. No math needed. It says 160 --
 4 MR. COHEN: Wait, wait, wait.
 5 He hadn't finished. Go ahead.
 6 A. Doses are typically expressed
 7 scientifically as milligrams per kilogram.
 8 BY MR. JANUSH:
 9 Q. It's 160 milligrams per
 10 5 milliliters, you see that above, under
 11 Infants Oral Suspension?
 12 A. Yes. What that means is you
 13 administer a volume of 5 milliliters that
 14 contains 160 milligrams.
 15 Q. Right.
 16 A. They also base this dosing on
 17 weight, right? Because scientifically, when
 18 you express a dose, it's milligrams per
 19 kilogram.
 20 Q. But they're giving an infant
 21 160 -- not an infant, a two- to
 22 three-year-old, a limitation of
 23 160 milligrams, and no such similar
 24 limitation exists for an adult, right? An
 25 adult dose is different and larger, true?

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1 A. We mean different things when
 2 we say "dose." As a toxicologist or
 3 pharmacologist, dose is normalized to body
 4 weight. This 160 number is not normalized to
 5 body weight. In fact, my guess -- again,
 6 I'm -- I don't work for the FDA, I don't work
 7 for J&J. I'm not a physician.
 8 My guess would be this is
 9 weight -- I mean, you have to, when the
 10 weight is different, you have to adjust the
 11 dose.
 12 Q. Right.
 13 A. So yes, this is not a surprise
 14 to me at all.
 15 Q. This is similar to allometric
 16 scaling, right? You're scaling down from an
 17 adult to a 24- to 35-pound toddler that's two
 18 to three years old and giving a lesser dose
 19 than the adult dose.
 20 MR. COHEN: Objection, form.
 21 A. No, this is not an example of
 22 allometric scaling. Not in any form.
 23 BY MR. JANUSH:
 24 Q. I said similar.
 25 A. I would not even characterize

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1 it as similar.
 2 Q. Okay. So when you say
 3 conversely, all drugs can be used safely at
 4 some dose, do you appreciate that there is a
 5 distinction of what a safe dose might be for
 6 a mother versus -- who is pregnant versus
 7 what the safe dose might be for her in utero
 8 developing baby that weighs far less than
 9 24 pounds?
 10 A. Let me preface this again: I'm
 11 not a physician. I'm not a pediatrician.
 12 I'm not an obstetrician. I can't comment
 13 much beyond saying -- pointing out the fact
 14 that you are -- you seem -- well, I'm sorry,
 15 I don't want to judge what you're trying to
 16 say.
 17 My understanding of what you're
 18 trying to say is that the dose that the
 19 mother takes, that's exactly what -- as long
 20 as the baby is in utero, that's what the baby
 21 sees. That's incorrect. The drug is
 22 distributed throughout the mother and the
 23 reproductive unit.
 24 So -- and, in fact, arguably,
 25 you could say that it's a lower dose than

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1 what an adult would normally get.
 2 Q. We're going to get there too.
 3 Promise you.
 4 (Whereupon, Deposition
 5 Exhibit P811, A simple practice guide
 6 for dose conversion between animals
 7 and human, by Nair et al., was marked
 8 for identification.)
 9 BY MR. JANUSH:
 10 Q. I was talking about allometric
 11 scaling with you a moment ago. I'm going to
 12 hand you P811. It's: A simple practice
 13 guide for dose conversion between animals and
 14 human.
 15 Have you ever seen this
 16 article, this journal that was -- this
 17 journal article published in the Journal of
 18 Basic and Clinical Pharmacy in 2016 --
 19 A. Not --
 20 Q. -- by Anroop Nair and Shery
 21 Jacob?
 22 A. Not to my recollection.
 23 Q. So if you turn to --
 24 MR. COHEN: Can he have just 30
 25 seconds to look at the document?

<p style="text-align: right;">Page 194</p> <p>1 MR. JANUSH: Yeah, sure.</p> <p>2 MR. COHEN: Thank you.</p> <p>3 (Document review.)</p> <p>4 BY MR. JANUSH:</p> <p>5 Q. And just to guide you with what</p> <p>6 I'm seeking to do here, I'm seeking to</p> <p>7 address the fact that there's a Table 1 with</p> <p>8 a human equivalent dose calculation and a</p> <p>9 Table 2 with an animal equivalent dose</p> <p>10 calculation or an AED.</p> <p>11 And for the moment, I only seek</p> <p>12 to address the notion that these authors have</p> <p>13 addressed how you scale a human equivalent</p> <p>14 dose based on body surface area and</p> <p>15 conversely or similarly, an animal equivalent</p> <p>16 dose calculation, which also includes human</p> <p>17 within the species to convert from.</p> <p>18 Do you see that?</p> <p>19 A. I'm sorry, specifically what --</p> <p>20 you're asking do I see the --</p> <p>21 Q. Do you see Table 2, human -- at</p> <p>22 the top of Table 2 and human at the top of</p> <p>23 Table 1. In other words, when you scale an</p> <p>24 HED, obviously humans are involved. When you</p> <p>25 scale an AED, an animal equivalent dose,</p>	<p style="text-align: right;">Page 196</p> <p>1 acetaminophen overdose in the liver, similar</p> <p>2 to the way it does in mice. That had been</p> <p>3 known for a long time. No one had shown it</p> <p>4 in mice previously.</p> <p>5 I'm sorry, that had been known</p> <p>6 for a long time in mice. No one had shown it</p> <p>7 in humans previously.</p> <p>8 Q. How many citations?</p> <p>9 A. Off the top of my head, I don't</p> <p>10 recall. Maybe 300 to 500, somewhere --</p> <p>11 Q. Yeah, that's what I saw when I</p> <p>12 looked at your highest work as well. And</p> <p>13 some of your other work, I saw less than a</p> <p>14 hundred for some, a hundred, 200 for one of</p> <p>15 them. Wouldn't surprise you of the numbers</p> <p>16 I'm saying, right?</p> <p>17 MR. COHEN: I'm sorry. Is this</p> <p>18 a question?</p> <p>19 BY MR. JANUSH:</p> <p>20 Q. In other words, range of</p> <p>21 between less than a hundred and 300 for</p> <p>22 citations of your literature is something</p> <p>23 you'd expect, right?</p> <p>24 MR. COHEN: Object to form.</p> <p>25 A. I have a number -- I mean, I</p>
<p style="text-align: right;">Page 195</p> <p>1 humans also can be involved in that</p> <p>2 conversion.</p> <p>3 Do you see that?</p> <p>4 A. I see the tables and I see the</p> <p>5 word "human" at the top lines.</p> <p>6 BY MR. JANUSH:</p> <p>7 Q. Incidentally, what's the most</p> <p>8 significant publication you've ever had</p> <p>9 that's been broadly accepted in the</p> <p>10 scientific community and cited in an</p> <p>11 incredible way, like high numbers? Do you</p> <p>12 know? Have you ever reviewed your literature</p> <p>13 to see how well you're cited?</p> <p>14 A. Because I have to provide</p> <p>15 certain metrics like citations and h-index</p> <p>16 and so on for, you know, faculty reviews,</p> <p>17 that sort of -- or annual reviews, that sort</p> <p>18 of thing, I do occasionally look.</p> <p>19 My highest cited original</p> <p>20 article is one that was published in 2012 in</p> <p>21 the Journal of Clinical Investigation, in</p> <p>22 which we demonstrated for the first time,</p> <p>23 using samples from humans -- acetaminophen</p> <p>24 overdose patients -- that mitochondrial</p> <p>25 damage also occurs in humans after</p>	<p style="text-align: right;">Page 197</p> <p>1 have many publications published over -- that</p> <p>2 have been available over different lengths of</p> <p>3 time and have accumulated different numbers</p> <p>4 of citations. You know, some of them are</p> <p>5 hundreds and hundreds and some haven't been</p> <p>6 cited yet.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. Okay. Want to take a guess how</p> <p>9 many times this Nair article has been cited,</p> <p>10 the simple practice guide for dose conversion</p> <p>11 between animals and humans?</p> <p>12 MR. COHEN: Object to form.</p> <p>13 BY MR. JANUSH:</p> <p>14 Q. Let me help you because I'm</p> <p>15 sure you don't want to guess. 812B.</p> <p>16 (Whereupon, Deposition</p> <p>17 Exhibit P812B, ReadCube Citation</p> <p>18 Reference, Nair article, was marked</p> <p>19 for identification.)</p> <p>20 BY MR. JANUSH:</p> <p>21 Q. 3,127 citations, according to</p> <p>22 ReadCube, but when you go on Google Scholar,</p> <p>23 3800 citations. That's a lot of citations</p> <p>24 for a concept that is nonsensical and not</p> <p>25 widely adopted, right?</p>

<p style="text-align: right;">Page 198</p> <p>1 MR. COHEN: Object to form.</p> <p>2 Is that a question?</p> <p>3 MR. JANUSH: It sure is.</p> <p>4 A. I'm happy to address this.</p> <p>5 First of all, the most widely accepted source</p> <p>6 for citation numbers is Web of Science.</p> <p>7 That's because --</p> <p>8 BY MR. JANUSH:</p> <p>9 Q. I'll give you my laptop. You</p> <p>10 want to do it with me?</p> <p>11 A. Please allow me to finish the</p> <p>12 question. We can do that if you like, but I</p> <p>13 have additional answers -- or additional</p> <p>14 parts to the answer.</p> <p>15 So it's well known that other</p> <p>16 citation databases, especially Google</p> <p>17 Scholar, overcount citations.</p> <p>18 In addition to that, a couple</p> <p>19 of other things. What you don't have in this</p> <p>20 information is whether or not those citations</p> <p>21 are positive or negative. For all I know,</p> <p>22 every single citation could be saying what</p> <p>23 these people say, don't do that, right? We</p> <p>24 have no way of knowing if the people citing</p> <p>25 them are affirming it in this room or</p>	<p style="text-align: right;">Page 200</p> <p>1 the FDA exists to protect human beings,</p> <p>2 right?</p> <p>3 MR. COHEN: Object to the form.</p> <p>4 BY MR. JANUSH:</p> <p>5 Q. It doesn't exist to protect</p> <p>6 mice, right?</p> <p>7 MR. COHEN: Object to the form.</p> <p>8 A. So I agree with your earlier</p> <p>9 statement and, in fact, that the FDA guidance</p> <p>10 document says this itself, that the purpose</p> <p>11 of human equivalent dosing is to protect the</p> <p>12 first-in-human subjects -- I'm not quite done</p> <p>13 with my answer.</p> <p>14 BY MR. JANUSH:</p> <p>15 Q. I didn't interrupt you. I'm</p> <p>16 just shaking my fingers.</p> <p>17 MR. COHEN: You are.</p> <p>18 MR. JANUSH: I'm not</p> <p>19 interrupting.</p> <p>20 MR. COHEN: So please don't</p> <p>21 shake your fingers at the witness.</p> <p>22 THE WITNESS: I take that as a</p> <p>23 sign --</p> <p>24 MR. JANUSH: No, no. Meaning</p> <p>25 like I want to talk in a moment. Go</p>
<p style="text-align: right;">Page 199</p> <p>1 rejecting it.</p> <p>2 Q. Actually, we do. Because</p> <p>3 there's also a --</p> <p>4 MR. COHEN: Were you done with</p> <p>5 your answer?</p> <p>6 THE WITNESS: No, I was not.</p> <p>7 MR. COHEN: So let him finish,</p> <p>8 please.</p> <p>9 A. Just give me a moment. I've</p> <p>10 lost my train of thought a bit here.</p> <p>11 Oh, in addition to that, as a</p> <p>12 scientist, it's not my practice and it's not</p> <p>13 common practice to judge the value of a</p> <p>14 publication based on citations, journal,</p> <p>15 authors, institutions. We judge it based on</p> <p>16 the content.</p> <p>17 I have no idea -- well, and the</p> <p>18 simple fact of the matter is I strongly</p> <p>19 disagree with this content, and the</p> <p>20 plaintiffs' experts cite the FDA guidance to</p> <p>21 endorse this kind of concept, but the FDA</p> <p>22 guidance absolutely does not endorse it. It</p> <p>23 says nothing about animal equivalent dosing.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. And again, you appreciate that</p>	<p style="text-align: right;">Page 201</p> <p>1 ahead.</p> <p>2 THE WITNESS: I apologize, I</p> <p>3 interpreted that as a sign that you</p> <p>4 wanted to speak. My mistake. Sorry,</p> <p>5 let me --</p> <p>6 A. So my question, then, is --</p> <p>7 there's a clear purpose for using that</p> <p>8 approach to go from animal studies to humans.</p> <p>9 What is the clear purpose from going from</p> <p>10 human doses to animals using this approach?</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. The clear purpose is that</p> <p>13 babies' lives are at stake. Do you</p> <p>14 understand that in this case?</p> <p>15 MR. COHEN: Object to the form.</p> <p>16 BY MR. JANUSH:</p> <p>17 Q. Babies' lives, their brains are</p> <p>18 at stake. So you test by looking at human</p> <p>19 doses and you apply that to animals so that</p> <p>20 you can get the best test you can, because</p> <p>21 there is something called a</p> <p>22 post-manufacturing and sale need for safety,</p> <p>23 isn't there, Doctor?</p> <p>24 MR. COHEN: Object to the form.</p> <p>25 A. I disagree with what you seem</p>

<p style="text-align: right;">Page 202</p> <p>1 to be defining as a human dose. You seem to</p> <p>2 be wholesale accepting that this animal</p> <p>3 equivalent dosing is the way to go and that</p> <p>4 these reflect human doses.</p> <p>5 There's an enormous problem</p> <p>6 with that in the case of acetaminophen. We</p> <p>7 know very well the pharmacokinetics, the</p> <p>8 blood concentrations, the duration of</p> <p>9 exposure that humans are exposed to at</p> <p>10 therapeutic doses of acetaminophen. There's</p> <p>11 no need to do this. We can just give</p> <p>12 different doses to mice and look at the</p> <p>13 plasma concentrations.</p> <p>14 Effectively, this has</p> <p>15 absolutely no applications to acetaminophen.</p> <p>16 Whether you agree with this approach or not</p> <p>17 in general, it is irrelevant for</p> <p>18 acetaminophen.</p> <p>19 BY MR. JANUSH:</p> <p>20 Q. Only acetaminophen or</p> <p>21 irrelevant in general? This human equivalent</p> <p>22 dose, this going back -- backwards to</p> <p>23 animals.</p> <p>24 A. Sorry. I -- just point of</p> <p>25 clarity because you said human equivalent</p>	<p style="text-align: right;">Page 204</p> <p>1 not a pediatrician. I'm not an obstetrician.</p> <p>2 I cannot --</p> <p>3 Q. You said the numbers are well</p> <p>4 known.</p> <p>5 MR. COHEN: Wait, were you</p> <p>6 finished?</p> <p>7 A. What I said is that, again,</p> <p>8 we're talking about maternal ingestion of</p> <p>9 therapeutic doses. We know very well the</p> <p>10 numbers with regard to duration of exposure,</p> <p>11 concentration and so on in women, including</p> <p>12 pregnant women, from some studies what</p> <p>13 concentrations to expect.</p> <p>14 What we're discussing here is</p> <p>15 about going back to animals, and what I'm</p> <p>16 saying is that this is totally unnecessary</p> <p>17 and not scientifically valid to go back to</p> <p>18 animal doses in the case of acetaminophen.</p> <p>19 BY MR. JANUSH:</p> <p>20 Q. At paragraph 22 of your report,</p> <p>21 moving back to your report, you wrote that:</p> <p>22 The toxicity of a drug is often organ</p> <p>23 specific. For example, the fact that</p> <p>24 acetaminophen overdose can cause injury to</p> <p>25 the liver does not mean that it also injures</p>
<p style="text-align: right;">Page 203</p> <p>1 dose. I'm referring to this idea of animal</p> <p>2 equivalent dosing.</p> <p>3 Q. I mean, they're the same</p> <p>4 concept, just addressed slightly different --</p> <p>5 A. No.</p> <p>6 Q. -- within the table, right?</p> <p>7 A. No, they're absolutely not the</p> <p>8 same concept. They use the same numbers to</p> <p>9 go back and forth, but again, the rationale</p> <p>10 for doing this to determine a human</p> <p>11 equivalent dose is clear. It's to protect</p> <p>12 first-in-human volunteers for these drugs.</p> <p>13 Going backwards from human</p> <p>14 doses to animals using similar numbers is</p> <p>15 totally unnecessary in cases when you have a</p> <p>16 well-characterized drug where you understand</p> <p>17 exposure, you understand plasma</p> <p>18 concentration, you understand the</p> <p>19 pharmacokinetics. That's the case with</p> <p>20 acetaminophen. This has no relevance to</p> <p>21 acetaminophen. It's unnecessary.</p> <p>22 Q. So what's an unsafe dose for a</p> <p>23 fetus based on all the knowledge you have as</p> <p>24 an acetaminophen expert?</p> <p>25 A. Yeah, I'm not a clinician. I'm</p>	<p style="text-align: right;">Page 205</p> <p>1 the brain. A liver is not a brain, and the</p> <p>2 brain does not play a major role in</p> <p>3 acetaminophen metabolism.</p> <p>4 Do you disagree with the notion</p> <p>5 that APAP overdose is often associated with</p> <p>6 neurological damage too?</p> <p>7 A. As I stated before, I'm not an</p> <p>8 epidemiologist. I cannot comment on the</p> <p>9 epidemiological associations.</p> <p>10 Q. No, that's actually not an</p> <p>11 epidemiological association. I'm talking</p> <p>12 about specific causation.</p> <p>13 Do you disagree that APAP</p> <p>14 overdose is associated with neurological</p> <p>15 damage?</p> <p>16 MR. COHEN: Object to the form.</p> <p>17 A. Look, this is not what I'm here</p> <p>18 to comment on. I was asked to address the</p> <p>19 questions that I've laid out in paragraph 4</p> <p>20 of my expert report.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. If a scientist was to opine</p> <p>23 that there's no neurological sequelae from</p> <p>24 acetaminophen overdose, that would be</p> <p>25 misleading, wouldn't it?</p>

<p>Page 206</p> <p>1 A. Again, I'm not here to address 2 neurodevelopmental or neurobehavioral 3 effects.</p> <p>4 Q. Do you agree that acetaminophen 5 increases both neuronal cytochrome P450 6 isoforms and CYP2E1 enzymatic activity and 7 protein levels?</p> <p>8 A. Absolutely not. At therapeutic 9 doses, absolutely not.</p> <p>10 Q. Are you aware of in vivo 11 experiments which show that intraperitoneal 12 administration of acetaminophen at 250- and 13 at 500-milligram per kilogram injection 14 induces neuronal death in the rat cortex?</p> <p>15 A. I'm aware of the Posadas study 16 that Louie referenced and that I believe you 17 are referring to.</p> <p>18 Q. And do you think it was just 19 done wrong?</p> <p>20 A. Yes.</p> <p>21 Q. The study was flawed?</p> <p>22 A. I would like to note that that 23 study was not designed to address any sort of 24 neurodevelopmental outcome. They were 25 interested in this idea that acetaminophen</p>	<p>Page 208</p> <p>1 requires to achieve hepatotoxicity. 2 In addition to that, what your 3 plaintiffs' experts have basically overlooked 4 or ignored is everything that occurs 5 downstream of NAPQI formation, with the 6 possible exception of some mentions of 7 oxidative stress here and there.</p> <p>8 A lot of other things happen, 9 right? We have mitochondrial damage. That 10 leads to oxidative stress. The oxidative 11 stress activates c-Jun N-terminal kinase by 12 causing it to dis -- causing ASK1 to 13 disassociate from thioredoxin.</p> <p>14 I'm sorry, I'm going to fast. 15 Let me slow down. So I'll restart.</p> <p>16 So after an overdose of 17 acetaminophen, you have NAPQI formation, 18 right, in the liver. That binds to 19 mitochondrial proteins. That leads to 20 mitochondrial dysfunction. Mitochondrial 21 dysfunction results in oxidative stress. The 22 oxidative stress leads to dissociation of 23 kinase -- an enzyme, protein for 24 simplicity -- called ASK1, from another 25 protein called thioredoxin that normally</p>
<p>Page 207</p> <p>1 may contribute to hepatic encephalopathy in 2 overdose patients. That's what they were 3 investigating.</p> <p>4 For the purposes of their 5 investigation, aside from the fact that they 6 used rats and, you know, which are not a good 7 species, generally speaking, for the study of 8 acetaminophen toxicity, I wouldn't 9 characterize it as a -- as a bad study for 10 that purpose. For the purpose that we're 11 addressing, it's a deeply flawed study.</p> <p>12 Q. When you say rats are not a 13 good species for acetaminophen testing, you 14 say that because rats have a very high 15 threshold to ward off hepatotoxicity, right?</p> <p>16 A. No, I say it for multiple 17 reasons. First of all, acetaminophen 18 metabolism in rats is not quite the same as 19 in humans or mice. They do more sulfation 20 than glucuronidation.</p> <p>21 In addition to that, the doses 22 that you have to give to -- kind of what 23 you're alluding to, the doses that you have 24 to give to rats to achieve hepatotoxicity are 25 far greater than what a human or mouse</p>	<p>Page 209</p> <p>1 sequesters it and holds it inactive. 2 When it dissociates, the ASK1, 3 through intermediary steps involving other 4 kinases, other proteins of the same type, 5 activates a kinase called the c-Jun 6 N-terminal kinase, or JNK for short.</p> <p>7 JNK then translocates to 8 mitochondria, where it binds to a protein 9 called Sab. Sab basically causes a change in 10 another protein called SHP, S-H-P. SHP then 11 dissociates -- or I'm sorry, let me rephrase 12 that. SHP then inhibits S-r-c or Src.</p> <p>13 Q. I think we're going to stop you 14 and call the judge. I think I've had it.</p> <p>15 Do you remember what my 16 question was?</p> <p>17 MR. COHEN: Object to the form. 18 MR. JANUSH: Yeah, my question 19 was -- 20 MR. COHEN: Hold on. Hold on. 21 MR. JANUSH: -- about rats. 22 MR. COHEN: You interrupted 23 him. Let's just get that on the 24 record. 25 MR. JANUSH: I have had enough,</p>

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1 man.

2 MR. COHEN: Let's just get it

3 out on the record.

4 BY MR. JANUSH:

5 Q. I don't want to hear your

6 soliloquies about all science. I want to

7 hear answers to my questions. I asked you

8 about rats being less hepatotoxic. That's

9 the whole question.

10 A. May I --

11 MR. COHEN: Hold on. Hold on.

12 Here's how it's going to work today.

13 You ask questions. You hear the

14 answer. You may not like it. You

15 don't interrupt him. Ask your next

16 question. Keep going. You've got

17 plenty of time.

18 THE WITNESS: I'd like to

19 continue my answer, if -- is that

20 okay?

21 MR. COHEN: Yeah.

22 MR. JANUSH: No, because I'm

23 just going to move to strike, and it's

24 going to get stricken, so it's wasting

25 your breath and my time.

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1 MR. COHEN: Well, you asked a

2 question that he -- he's obligated to

3 give a complete and full answer to

4 your questions, just as your experts

5 did. And he's going to do that.

6 Now, if you don't want to do

7 that and want to end the deposition,

8 that's your choice.

9 THE WITNESS: I'm --

10 MR. JANUSH: If you would like

11 to continue to filibuster, you do

12 that. I will write my letter to the

13 Court if I need to.

14 MR. COHEN: That is an

15 inappropriate comment, just as many of

16 the other comments you've made today.

17 Please be a little more professional.

18 THE WITNESS: I'm getting to

19 the answer to your question.

20 A. So you asked -- my

21 understanding of your question is that -- is

22 why do we think rats are a poor model for

23 acetaminophen toxicity, right?

24 I'm telling you the mechanisms

25 that we know occur in humans and in mice.

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1 The mechanisms in humans and mice so far

2 appear to be identical from all the available

3 data, and I'm trying to explain what's

4 different in rats, okay?

5 So essentially, much of these

6 downstream effects -- here we're just talking

7 about, for the most part, plaintiffs' experts

8 and myself have just addressed the NAPQI

9 formation, a little bit about oxidative

10 stress.

11 What I'm trying to convey is

12 that there are many other events in the

13 mechanism of toxicity, and some of those

14 additional events in rats do not resemble

15 what we know to occur in humans and mice.

16 That's why, for those three

17 reasons, the resistance to hepatotoxicity

18 requiring higher doses, differences in

19 metabolism and differences in mechanistic --

20 other mechanistic endpoints, that's why we

21 don't consider rats a good model for human

22 acetaminophen hepatotoxicity.

23 BY MR. JANUSH:

24 Q. Okay. When you're speaking in

25 front of an audience, you've acknowledged

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1 that rats are not a good model because they

2 are so resistant to acetaminophen toxicity,

3 right? It's just a yes or no.

4 When you've spoken in front of

5 people as a panelist, that's what you've

6 acknowledged in simple terms in one straight

7 sentence, right?

8 MR. COHEN: I'm sorry, object

9 to the form. This is improper

10 deposition conduct. You can't tell a

11 witness, say yes or no. Just ask your

12 question.

13 MR. JANUSH: I can --

14 MR. COHEN: He'll give you his

15 answer. And then if you don't like

16 it, you can ask another question, you

17 can move to strike, but please, don't

18 lecture him all day on how he should

19 be answering questions. It's

20 inappropriate conduct, Counsel.

21 BY MR. JANUSH:

22 Q. Sir, can you answer my

23 question?

24 A. Your question is -- I just want

25 to make sure I understand.

<p style="text-align: right;">Page 214</p> <p>1 Q. When you've been a panelist, in 2 plain, unspoken, simple terms, you've set 3 forth in one sentence why rats are not a good 4 model for testing on acetaminophen, right? 5 A. I don't recall every single 6 public speaking engagement I've had or what I 7 said in every single one. However, making 8 that one statement, first of all, it doesn't 9 preclude other reasons, and second of all, 10 when you're speaking in front of people, 11 there's usually a time limit or some sort of 12 expectation for time, and I'm not necessarily 13 going to go into a long monologue on every 14 possible reason. It's usually sufficient for 15 those purposes to just give one or two and 16 move on. 17 Q. Okay. We're going to play a 18 video clip. We're going to mark this as 19 Exhibit 870. 20 (Whereupon, Deposition 21 Exhibit P870, Media File, Measuring 22 Toxicity Biomarkers, was marked for 23 identification.) 24 (Whereupon, Exhibit 870 was 25 played aloud in the deposition room.)</p>	<p style="text-align: right;">Page 216</p> <p>1 Posadas paper, in fact, because you can look 2 at the plasma concentrations that those doses 3 resulted in, and they are 1 millimole per 4 liter to two millimoles per liter. 5 Just for reference, the maximum 6 therapeutic concentration that you typically 7 achieve at a -- with a dose of Extra Strength 8 Tylenol is around 132 micromoles per liter. 9 So 1 to 2 millimole per liter is 1,000 to 10 2,000 micromoles per liter. That absolutely 11 cannot be said to mimic human exposure to 12 acetaminophen at therapeutic doses. 13 Those are extremely high 14 concentrations. Those are the concentrations 15 you see in a human at overdose. 16 Q. Actually, I'm thinking that the 17 math is done wrong here because Posadas found 18 that acetaminophen can cause 19 concentration-dependent neuronal death in 20 vitro at concentrations, as you said, of 1 21 and 2 millimolar per millimeter [sic], but 22 that's well below the stated concentrations 23 observed in humans, which ranges from 66 to 24 198 micromolars, right? 25 MR. COHEN: Object. We don't</p>
<p style="text-align: right;">Page 215</p> <p>1 BY MR. JANUSH: 2 Q. So I just want to ask: Was 3 that you that we just heard speaking? 4 A. It sounds like me and I recall 5 this webinar. 6 Q. Okay. Thank you. 7 MR. COHEN: When it's 8 convenient, let us know if you want 9 to -- when you want to take a break. 10 It's over an hour. 11 MR. JANUSH: I don't want to, 12 but if you'd like to, I will 13 accommodate, absolutely. 14 MR. COHEN: When you get to a 15 breaking point. 16 MR. JANUSH: Okay. 17 BY MR. JANUSH: 18 Q. By the way, going back to 19 Posadas. Posadas 2010 was testing rats at 20 250 and 500 milligrams per kilogram, far less 21 than the toxic doses that you just -- that we 22 just played from your presentation, right? 23 A. Again, a sub-hepatotoxic dose, 24 the term is not interchangeable with 25 therapeutic dose. That's very clear in the</p>	<p style="text-align: right;">Page 217</p> <p>1 have Posadas marked. 2 MR. JANUSH: Don't need to. 3 I'm just talking about the math here. 4 MR. COHEN: No, you're talking 5 about Posadas. 6 THE WITNESS: Yeah, I don't 7 know what you're reading from. 8 BY MR. JANUSH: 9 Q. These are my notes, not 10 Posadas. 11 A. May I hear the question again? 12 Q. Sure. 13 MR. COHEN: Are you relying on 14 Posadas? Because if you are, maybe 15 you can hand it to him and you can 16 simplify this. 17 MR. JANUSH: You can say 18 objection, form only and not coach. I 19 don't need to hand a document over 20 when I want to question about a topic. 21 I don't need to. 22 MR. COHEN: That's 23 inappropriate conduct. 24 A. If we're asking a question -- 25 MR. JANUSH: It's not</p>

<p style="text-align: right;">Page 218</p> <p>1 inappropriate. You just coached your 2 witness to ask for a document. 3 MR. COHEN: That's nonsense. 4 MR. JANUSH: That is absolutely 5 what you did. The depo protocol is 6 "objection, form." If he needs to see 7 something, he's a real bright guy, he 8 can ask me for it. 9 BY MR. JANUSH: 10 Q. Witness, let's go back, 11 Dr. McGill to my question: Posadas -- do you 12 know whether Posadas 2010 found that 13 acetaminophen can cause 14 concentration-dependent neuronal death in 15 vitro at concentrations 1 and 2 millimolars 16 per milliliter? 17 MR. COHEN: Objection, form. 18 A. I would like to see the paper 19 since you are asking me specific questions 20 about it. I don't recall off the top of my 21 head at what dose they claim to have observed 22 neuronal toxicity. 23 The doses that they 24 administered to rats, which is what they used 25 to guide their in vitro dosing per my</p>	<p style="text-align: right;">Page 220</p> <p>1 your report -- 2 MR. COHEN: I'm sorry. 3 MR. JANUSH: No, no. This is 4 unfair now. 5 MR. COHEN: You just 6 interrupted him. 7 MR. JANUSH: He can't talk 8 about my expert when asked about what 9 is in his report. 10 MR. COHEN: I'm sorry, you 11 cannot interrupt the witness. Just 12 let him answer and ask the next 13 question. 14 A. My -- my report is, in part at 15 least, a response to the plaintiffs' experts, 16 so I think it's reasonable, necessary in this 17 case, to reference the plaintiffs' experts' 18 opinions or speculation, really. 19 So the plaintiffs' experts have 20 speculated on a few possible mechanisms. 21 That's what I was asked to address. 22 So when I look at the data with 23 respect to those possible mechanisms, the 24 speculative mechanisms by which the 25 plaintiffs' experts opine acetaminophen might</p>
<p style="text-align: right;">Page 219</p> <p>1 recollection of the paper, that resulted in 2 plasma concentrations of 1 to 2 millimole per 3 liter, which is the same as 1,000 to 2,000 4 micromoles per liter, which is much higher 5 than the human therapeutic exposure -- 6 maximum human therapeutic exposure of around 7 130 micromoles per liter. 8 BY MR. JANUSH: 9 Q. What literature can you point 10 to that concludes, if you solely look at how 11 acetaminophen poses hepatic effects, you can 12 extrapolate what the effect of acetaminophen 13 will be on the human brain? 14 A. That is a very broad question. 15 I mean... 16 Q. Looking at your report, what 17 have you cited to in your expert report that 18 helps you conclude that if you look at how 19 acetaminophen poses hepatic effects, you can 20 extrapolate what the effect of acetaminophen 21 will be on the human brain? 22 A. Your expert -- I'm sorry, I 23 don't mean to say "your." 24 Q. Not my expert. We're talking 25 about you. What can -- did you point to in</p>	<p style="text-align: right;">Page 221</p> <p>1 cause toxicity in the brain, we just see no 2 evidence to support it. 3 There's -- as I've laid out in 4 my report, there's very, very little CYP2E1 5 in the brain relative to the liver. Those 6 studies in which they have looked at, you 7 know, acetaminophen-protein adducts in the 8 brain have found none, and yeah, there's 9 just -- so I was asked to address those 10 issues. That's what I've done in my report. 11 I find that the data don't support the claims 12 of the plaintiffs' experts. 13 MR. COHEN: Is this a 14 convenient moment to break? 15 MR. JANUSH: It sure is. 16 Whenever you would like. 17 MR. COHEN: Thank you. 18 THE VIDEOGRAPHER: We are going 19 off record. The time is 1:37. 20 (Recess taken, 1:37 p.m. to 21 1:54 p.m. CDT) 22 THE VIDEOGRAPHER: We're going 23 back on record. The time is 1:54. 24 BY MR. JANUSH: 25 Q. Dr. McGill, I'm going to have</p>

<p style="text-align: right;">Page 222</p> <p>1 you turn to your report at page 18, the</p> <p>2 second paragraph of -- or second portion of</p> <p>3 paragraph 29. Let me know when you're there.</p> <p>4 A. I'm there.</p> <p>5 Q. Okay. I'm reading from the</p> <p>6 second line down: Glutathione is available</p> <p>7 in sufficient amounts in the liver to</p> <p>8 detoxify NAPQI after human therapeutic doses</p> <p>9 of acetaminophen.</p> <p>10 Do you see that?</p> <p>11 A. Yes.</p> <p>12 Q. Is that statement true, in your</p> <p>13 opinion, for in utero fetuses exposed to an</p> <p>14 adult dose of acetaminophen in the second</p> <p>15 trimester?</p> <p>16 A. So in my expert report, I</p> <p>17 reference -- or it briefly describes a number</p> <p>18 of studies that measured glutathione in the</p> <p>19 human brain, including a couple that looked</p> <p>20 at the fetus. I -- off the top of my head I</p> <p>21 don't recall exactly what trimester, but they</p> <p>22 did show that there was millimole per liter</p> <p>23 quantities of glutathione in the fetal brain</p> <p>24 just like the adult brain.</p> <p>25 Q. So do you believe that in utero</p>	<p style="text-align: right;">Page 224</p> <p>1 I have to find it again.</p> <p>2 Q. And what page are you on?</p> <p>3 A. Ah. So this is the Raijmakers.</p> <p>4 It's page 41.</p> <p>5 Q. Uh-huh.</p> <p>6 A. And I haven't looked through</p> <p>7 all of these, so I'm not sure if --</p> <p>8 Q. Let me just ask something on</p> <p>9 Raijmakers since you cited it as a relevant</p> <p>10 study.</p> <p>11 Zero acetaminophen tested in</p> <p>12 Raijmakers, right? Absolutely none, right?</p> <p>13 A. To my recollection, they</p> <p>14 weren't looking at acetaminophen, right.</p> <p>15 They were looking at glutathione levels.</p> <p>16 Q. So it -- it's -- it can't be a</p> <p>17 relevant study in response to my question if</p> <p>18 my question was, quote: Is that statement</p> <p>19 true in your opinion for in utero fetuses</p> <p>20 exposed to an adult dose of acetaminophen in</p> <p>21 the third trimester?</p> <p>22 A. Well, I disagree with your</p> <p>23 statement it can't be relevant. What they've</p> <p>24 demonstrated is that there is glutathione in</p> <p>25 the liver, in the fetus. Generally speaking,</p>
<p style="text-align: right;">Page 223</p> <p>1 fetuses exposed to an adult dose of</p> <p>2 acetaminophen in the third semester has</p> <p>3 sufficient glutathione available in the liver</p> <p>4 to detoxify NAPQI after human therapeutic</p> <p>5 doses of acetaminophen?</p> <p>6 A. So now you're asking third</p> <p>7 trimester in the liver?</p> <p>8 Q. I am.</p> <p>9 A. So I'm trying to recall studies</p> <p>10 that I cited with respect to glutathione</p> <p>11 measurement in -- in vivo that may -- that</p> <p>12 involved fetal measurement.</p> <p>13 (Document review.)</p> <p>14 A. So in at least one of the</p> <p>15 studies that I cited in my report, they were</p> <p>16 able to detect glutathione levels in the</p> <p>17 liver of the fetus, so it is present. I</p> <p>18 would expect it to be present, again, at</p> <p>19 millimolar concentration.</p> <p>20 Q. Was there -- what study was</p> <p>21 that that you're relying on, that one study?</p> <p>22 A. That particular one that I was</p> <p>23 looking at --</p> <p>24 Q. Yeah.</p> <p>25 A. -- at that moment -- I'm sorry,</p>	<p style="text-align: right;">Page 225</p> <p>1 glutathione is present at millimole per liter</p> <p>2 concentrations in the liver and throughout</p> <p>3 the body. Millimole per liter concentrations</p> <p>4 are high biologically. It's quite high.</p> <p>5 So if there's glutathione</p> <p>6 present, then I would absolutely expect it to</p> <p>7 detoxify NAPQI.</p> <p>8 Q. And for that opinion, you would</p> <p>9 look to Raijmakers et al. on page 41?</p> <p>10 A. A number of studies. So every</p> <p>11 study that I'm aware of that has measured</p> <p>12 glutathione in tissues throughout the body,</p> <p>13 whether we're talking about brain, liver, any</p> <p>14 other tissue, including this study, has</p> <p>15 found, although -- well, has found high</p> <p>16 millimole per liter concentrations.</p> <p>17 So I'm relying on -- this is</p> <p>18 one study that I've specifically pointed out</p> <p>19 as an example in response to your question,</p> <p>20 but there are numerous studies that support</p> <p>21 what I just said.</p> <p>22 Q. And if we move forward to</p> <p>23 Acetaminophen Pharmacokinetics During</p> <p>24 Pregnancy at page 20, this is a section where</p> <p>25 you're addressing: Published studies</p>

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1 reporting differences in acetaminophen
2 metabolism and pharmacokinetics between
3 pregnant and nonpregnant women that are
4 unlikely to have significant clinical impact.
5 No published study provides direct data on
6 embryonic/fetal acetaminophen metabolism in
7 humans. Major studies reporting data on
8 acetaminophen in pregnancy are described
9 below.

10 Right? That's what you're
11 addressing in this section?

12 A. Well, you've read what I've
13 written.

14 Q. Okay. So let's go to
15 paragraph 32 where you address that:
16 Acetaminophen must traverse the
17 blood-placenta barrier to reach the embryo or
18 fetus.

19 And you write: Acetaminophen
20 has been shown to cross the placenta after
21 maternal use.

22 And I'm going to skip the next
23 sentence and address: However, acetaminophen
24 concentrations in umbilical cord blood after
25 maternal ingestion of therapeutic doses have

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1 been reported to be nearly identical to the
2 low concentrations in maternal blood,
3 prompting the conclusion that maternal use of
4 acetaminophen at the currently recommended
5 dose is unlikely to lead to accumulation of
6 potentially toxic levels in the fetus.

7 Did I read that correctly?

8 A. Yes.

9 Q. Okay. And after making that
10 last statement, you cite to a single case
11 reported at footnote 50. It's the Nitsche
12 study, right?

13 A. That is what's listed for the
14 footnote.

15 Q. Okay. And this concerned a
16 neonate to address -- and you used this study
17 to address that maternal use of acetaminophen
18 at the currently recommended dose is unlikely
19 to lead to accumulation of potentially toxic
20 levels in the fetus. Right?

21 A. That's a quote from that study.
22 It's not my words.

23 Q. Right. I understand that.
24 Dr. McGill, I'm going to
25 provide you with -- where is 813? I'm going

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1 to provide you with 813.
2 (Whereupon, Deposition
3 Exhibit P813, Transplacental Passage
4 of Acetaminophen in Term Pregnancy, by
5 Nitsche et al., was marked for
6 identification.)
7 BY MR. JANUSH:
8 Q. This is the Nitsche study.
9 It's Transplacental Passage of Acetaminophen
10 in Term Pregnancy. It's published
11 November 2016 online, and let me ask you
12 something.
13 What was the goal of the
14 Nitsche-cited -- Nitsche study you cited, or
15 stated differently -- let me help on this.
16 This was the study, was it not,
17 where pregnant women undergoing scheduled
18 cesarean section deliveries were given a dose
19 of 1,000 milligrams of acetaminophen just
20 before they gave birth, and the acetaminophen
21 levels were then tested in the mother and
22 neonate as soon as 30 minutes after the
23 maternal administration of the drug, right?
24 A. If you don't mind, I'd like a
25 little bit of time to refresh myself.

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1 Q. Sure. And just to give you
2 guidance on where I was addressing that from,
3 it was the second page, center of the left
4 side, starting with "Acetaminophen is widely
5 used in pregnancy."
6 But really, I'm addressing the
7 language: This report suggests that the
8 level attained in the neonate after a single
9 maternal dose of acetaminophen is similar to
10 the levels obtained after an oral dose
11 administered directly to the neonate.
12 And then if you look at the
13 study design just below, you'll see the 1,000
14 milligrams, single oral dose upon admission
15 for scheduled cesarean section -- cesarean
16 section.
17 Do you see that, a few
18 sentences down from the word "study design"
19 in big bold letters? And it's also on the
20 screen to guide you in front of you, to
21 prompt you. You should definitely allow the
22 screen to help you. It will help.
23 (Document review.)
24 BY MR. JANUSH:
25 Q. And if we turn to the third

<p style="text-align: right;">Page 230</p> <p>1 page, and it's the final page. It's a real 2 short study. At the Conclusion: Maternal 3 and fetal acetaminophen levels are comparable 4 as early as 30 minutes after administration, 5 indicating rapid placental transfer of the 6 drug. 7 Notably, acetaminophen PKs in 8 fetal samples closely parallels behavior of 9 the drug in the maternal system. The time to 10 peak concentration and half-life are similar, 11 and the fetal AUC is nearly the same as the 12 maternal AUC. 13 Do you see that? 14 A. I see the statements. 15 Q. Okay. 16 A. I'd like to note, these are 17 technically not fetal samples, right? 18 They're neonates who were delivered by 19 cesarean section, so we're talking about 20 exposure very late in pregnancy at the time 21 of delivery. 22 Q. Right. 23 A. This is not fetal development, 24 it's not embryonic development. 25 Q. Right. Yeah. And you cited to</p>	<p style="text-align: right;">Page 232</p> <p>1 this study. It's a direct quote from the 2 study. 3 Q. I understand. 4 But when you take a quote from 5 the study and include it as a concluding 6 sentence in a paragraph, you are adopting 7 their conclusion in your report, right? 8 You're not saying anywhere here 9 "and I disagree with this conclusion," are 10 you? 11 A. My statement was that the data 12 prompted the authors to conclude, and then I 13 directly quoted them. 14 Q. Right. 15 A. I was saying that it prompted 16 them to conclude it. I wasn't saying it was 17 my conclusion. 18 Q. Okay. 19 A. I think it's a reasonable 20 conclusion. 21 Q. You do? 22 A. From the data in that study. 23 Q. Okay. So -- 24 A. And from the other data that 25 I've seen.</p>
<p style="text-align: right;">Page 231</p> <p>1 this, not me, right? 2 A. Yes, I cited to it. 3 Q. Okay. So -- and you cited to 4 it as relevant to your expert report in a 5 case involving fetal neurodevelopmental 6 issues, right? 7 A. I cited to it as relevant data 8 showing that there's transplacental passage 9 of acetaminophen. 10 Q. Okay. 11 A. But again, I didn't say that 12 these should -- I didn't say that this study, 13 in my report, does or does not comment on the 14 embryonic or fetal development. It does not. 15 This is neonatal. 16 Q. Understood. 17 A. But I didn't state that in the 18 report. 19 Q. But you did say -- you did say 20 "prompting the conclusion that maternal use 21 of acetaminophen at the currently recommended 22 dose is unlikely to lead to accumulation of 23 potentially toxic levels in the fetus." 24 You did say that, right? 25 A. I was quoting the authors of</p>	<p style="text-align: right;">Page 233</p> <p>1 Q. So help me on this, because 2 would you agree with the notion that 3 prompting the conclusion that this 4 recommended dose is unlikely to lead to 5 accumulation of potentially toxic levels in 6 the fetus, that conclusion is addressing a 7 safety issue, right, toxic levels in the 8 fetus? 9 MR. COHEN: Object -- 10 BY MR. JANUSH: 11 Q. Fair to say? 12 MR. COHEN: Object to the form. 13 A. I can't comment on what the 14 authors intended to convey with that 15 statement. 16 BY MR. JANUSH: 17 Q. Okay. Well, let's comment on 18 what you can address. 19 Can you point to any studied 20 endpoints in this three-page piece of 21 literature that addresses where the authors 22 were studying safety to the fetus? Anywhere? 23 MR. COHEN: Object to the form. 24 BY MR. JANUSH: 25 Q. I mean, I -- the reason I'm</p>

<p style="text-align: right;">Page 234</p> <p>1 asking is I only see discussion concerning 2 the levels of acetaminophen observed just 3 after cesarean section. So I'd like to know 4 how the authors could have arrived at a 5 safety conclusion in the absence of endpoints 6 on safety. 7 MR. COHEN: Object to the form. 8 Go ahead. 9 A. I can't comment on the authors' 10 thought process. My understanding of what 11 they're trying to say is that the -- from the 12 data available in this manuscript, the 13 pharmacokinetics, or at least plasma 14 concentrations of acetaminophen, appear to be 15 similar in the mother and the neonate at the 16 time of delivery. And I suppose they're 17 making the assumption that you can 18 extrapolate that to earlier fetal 19 development. 20 BY MR. JANUSH: 21 Q. Well -- 22 A. And we know that those 23 therapeutic blood concentrations in the 24 mother are deemed safe. Those are the -- 25 that's a -- the 1-gram dose is what is</p>	<p style="text-align: right;">Page 236</p> <p>1 acetaminophen-protein binding in the brain, 2 indicating no NAPQI formation in the brain. 3 The literature also show that 4 there is no -- or that there is glutathione 5 present in the -- in the brain, including the 6 fetal brain, and so -- and databases show 7 that also the low levels -- little to no 8 CYP2E1 present in the brain extends to 9 human -- different stages of human fetal 10 development. 11 So when you put that all 12 together with the fact that there's extremely 13 low to no potential for NAPQI formation in 14 the brain, even if it did form, there's 15 glutathione to scavenge it. And we know that 16 that works really well with these 17 concentrations of acetaminophen in adults. 18 There's no reason to think it wouldn't also 19 work very well at these concentrations in 20 the -- in the child. 21 BY MR. JANUSH: 22 Q. You just assumed a lot as to 23 what the authors were concluding, didn't you? 24 MR. COHEN: Object to form. 25 A. I was giving my opinion that</p>
<p style="text-align: right;">Page 235</p> <p>1 recommended by the manufacturer and what the 2 FDA allows, so it's considered a safe dose, 3 and they get the same blood concentration. 4 So I think that's the reasoning 5 of the authors, but again, it's the authors' 6 reasoning. 7 BY MR. JANUSH: 8 Q. Yes, I get you. You quoted 9 this, though, to address that the authors 10 concluded that maternal use of acetaminophen 11 at the currently recommended dose is unlikely 12 to lead to accumulation of potentially toxic 13 levels in the fetus, and I'm just asking you 14 to point me to where toxicity was studied, if 15 at all. 16 It wasn't here, right? I mean, 17 it's a simple issue. I'm just asking you if 18 you agree that it wasn't studied here. 19 MR. COHEN: Objection, form. 20 A. I think you have to take it in 21 the context of the greater literature, right? 22 The greater literature, as I've described in 23 my report, shows that there is little to no 24 CYP2E1 in the brain, so there's no -- also -- 25 the literature also show there's no</p>	<p style="text-align: right;">Page 237</p> <p>1 the data have to be interpreted within the 2 greater context of the literature. I can't 3 say the authors did that or not. Within the 4 greater context of the literature, their 5 conclusion was reasonable, however. 6 BY MR. JANUSH: 7 Q. Well, let's talk about what the 8 authors actually said, because they said 9 something vastly different from what you 10 said. 11 Last paragraph: Although the 12 current study suggests that fetal exposure to 13 acetaminophen can be predicted using maternal 14 drug levels, further study of acetaminophen 15 metabolism to NAPQI in the fetus is clearly 16 needed to better understand the risk of fetal 17 harm after maternal acetaminophen use. 18 You see that? 19 A. I see their statement. 20 Q. It's very different from what 21 you just said, right, about the body of 22 literature that you take into consideration 23 to conclude safety? 24 A. Well, again, I can't say what 25 the authors were thinking or what the</p>

<p style="text-align: right;">Page 238</p> <p>1 rationale was at the time.</p> <p>2 Q. You can. It's in black and</p> <p>3 white, right, on this page?</p> <p>4 A. No, no. They haven't said how</p> <p>5 they arrived at their conclusion based on</p> <p>6 these data, other than we know these levels</p> <p>7 are safe in adults, probably safe in the</p> <p>8 fetus too; or rather, the levels in the</p> <p>9 neonates was not higher than what you see in</p> <p>10 adults. So that's part of their reasoning.</p> <p>11 I can't comment on the rest of their</p> <p>12 reasoning.</p> <p>13 Q. Do these authors demonstrate</p> <p>14 that the neonate is able to maintain high</p> <p>15 doses, high levels of -- to counter repeated</p> <p>16 exposures, high levels of NAPQI?</p> <p>17 A. I'm sorry, you --</p> <p>18 Q. I mean of -- yes, that is what</p> <p>19 I mean.</p> <p>20 A. I don't think the question</p> <p>21 makes sense.</p> <p>22 Q. I mean glutathione. I meant to</p> <p>23 say glutathione. Sorry.</p> <p>24 MR. COHEN: Can you repeat the</p> <p>25 question?</p>	<p style="text-align: right;">Page 240</p> <p>1 database, their LMD microarray database, and</p> <p>2 from one of the studies I cited in my report,</p> <p>3 one of the publications, that fetal</p> <p>4 expression of P450s in the brain is still</p> <p>5 very low compared to the liver.</p> <p>6 So given that information,</p> <p>7 there's glutathione present, there's very</p> <p>8 little P450. We have not only no reason to</p> <p>9 believe that they would have toxic effects;</p> <p>10 we have strong reason to doubt that there</p> <p>11 would be toxic effects in the fetus in the</p> <p>12 brain.</p> <p>13 Q. So I'm going to circle back to</p> <p>14 Rajmakers in a moment. I want to go to the</p> <p>15 last sentence of this paragraph: However,</p> <p>16 our findings suggest that maternal use of</p> <p>17 acetaminophen at the currently recommended</p> <p>18 dose is unlikely to lead to accumulation of</p> <p>19 potentially toxic levels in the fetus.</p> <p>20 Do you see that?</p> <p>21 A. I see the statement.</p> <p>22 Q. What are their findings that</p> <p>23 they're pointing to in this literature?</p> <p>24 A. Again, I can't comment on --</p> <p>25 Q. I mean, you used the</p>
<p style="text-align: right;">Page 239</p> <p>1 MR. JANUSH: I apologize.</p> <p>2 BY MR. JANUSH:</p> <p>3 Q. I meant to simply say: Do you</p> <p>4 believe that there's sufficient levels of</p> <p>5 glutathione in a neonate to endure repeated</p> <p>6 exposures at this level in utero with no</p> <p>7 downstream neurotoxic effects?</p> <p>8 A. Well, again, I can't comment on</p> <p>9 these neurodevelopmental outcomes. Do I --</p> <p>10 if the question is do I believe there's</p> <p>11 glutathione -- sorry, were you asking in the</p> <p>12 brain or the liver?</p> <p>13 Q. Brain of the baby.</p> <p>14 A. In the brain of the baby.</p> <p>15 Well, in fact, we know there's glutathione in</p> <p>16 the brain of the baby. I mentioned that</p> <p>17 Rajmakers study, right.</p> <p>18 Q. Uh-huh.</p> <p>19 A. So -- and in fact, in that</p> <p>20 study, they actually noted that the</p> <p>21 concentration in the brain was higher than</p> <p>22 the concentration in the fetal liver. So</p> <p>23 there's clearly glutathione present.</p> <p>24 We also know from, for example,</p> <p>25 the Allen Institute for Brain Sciences</p>	<p style="text-align: right;">Page 241</p> <p>1 literature, so I'm -- do you read literature</p> <p>2 constructively when you cite it in an expert</p> <p>3 report?</p> <p>4 MR. COHEN: Object to form.</p> <p>5 A. I cannot comment on the</p> <p>6 rationale of the authors at that time.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. Did you read literature</p> <p>9 constructively to determine, gee, did the</p> <p>10 authors get this right? Did they have actual</p> <p>11 data to support their conclusion?</p> <p>12 Do you do that?</p> <p>13 MR. COHEN: Objection, form.</p> <p>14 A. Their data are consistent with</p> <p>15 my -- with the information in my report. I</p> <p>16 cannot comment on what they were thinking at</p> <p>17 the time.</p> <p>18 BY MR. JANUSH:</p> <p>19 Q. I'm not talking about their</p> <p>20 data about the acetaminophen passing from the</p> <p>21 mother to the baby in doses that mirror the</p> <p>22 mother. That -- that is not what I'm talking</p> <p>23 about.</p> <p>24 I'm talking about their data</p> <p>25 regarding a safety point. Where is the</p>

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1 safety data in this three-page study? Can
 2 you point me to it?
 3 Because the way I'm reading
 4 this, I see a conclusion about our findings,
 5 quote. And I don't see findings about
 6 safety. So I'm trying to find whether this
 7 was a gratuitous statement and that -- or
 8 not. And I'd like your guidance on that.
 9 A. I can tell you how I would
 10 interpret this in the context of the greater
 11 literature -- as I mentioned, how I interpret
 12 it in the context of the greater literature
 13 as evidence for safety. I can't comment on
 14 what they were thinking at the time.
 15 Q. But you do see that they wrote
 16 our findings. In other words, they weren't
 17 looking at the body of literature. They were
 18 looking at our findings.
 19 A. Okay. So one issue with that
 20 is they may have other findings than what's
 21 in this report, right. I can't say off the
 22 top of my head.
 23 Q. How do you feel comfortable
 24 citing to this piece of literature --
 25 MR. COHEN: Object to the form.

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1 BY MR. JANUSH:
 2 Q. -- for safety -- to include the
 3 safety conclusion at footnote 32, when
 4 there's no safety endpoints addressed in the
 5 literature?
 6 A. Yeah, as I explained, all the
 7 literature that I've -- as I've described in
 8 my report, all the literature show there is
 9 little to no CYP2E1 in the brain, there is no
 10 NAPQI formation or presence in the brain.
 11 There is glutathione in the brain that is
 12 available to scavenge NAPQI if any did form.
 13 And so when you take that with
 14 the fact that the concentrations to which the
 15 fetus -- well, in this case, again, this is
 16 neonates. It's not really fetus, but fine --
 17 to which the fetus was exposed is similar to
 18 what we're exposed to, then there's simply no
 19 reason -- taken as a bigger picture, it's
 20 strong evidence for the safety of -- for the
 21 safety of the fetus with this exposure to
 22 acetaminophen, with maternal ingestion of
 23 therapeutic doses of acetaminophen.
 24 Q. You mentioned the Rajmakers
 25 study. Wasn't that of only two fetuses?

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1 A. I don't recall off the top of
 2 my head. You'd have to show me the report.
 3 Q. I mean, you were referencing it
 4 from your report as something supportive of
 5 your opinions, so I'm just drilling down.
 6 A. I'm happy to comment on it if
 7 you can produce a copy of the paper.
 8 Q. I can't. Rajmakers -- do you
 9 remember if Rajmakers completely failed to
 10 look at any regenerative capabilities of
 11 glutathione?
 12 MR. COHEN: Object -- object to
 13 the form.
 14 A. Again, if you produce a copy of
 15 the paper, I'll be happy to comment on it.
 16 BY MR. JANUSH:
 17 Q. In Rajmakers, do you remember
 18 that there was absolutely no indication
 19 whatsoever as to whether acetaminophen had
 20 been used before there was testing done?
 21 MR. COHEN: Object to the form.
 22 A. Again, if you produce a copy of
 23 the paper, I'm happy to comment on it.
 24 BY MR. JANUSH:
 25 Q. It's something you cited, sir,

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1 so I'm just coming back to you on whether you
 2 know your own literature that you cited.
 3 MR. COHEN: Object to the form.
 4 A. I cited it because it shows
 5 that there is glutathione present in the
 6 fetal brain and as well as the fetal liver.
 7 BY MR. JANUSH:
 8 Q. I think it's going to be
 9 important to the court in this case as to
 10 whether you were citing literature that was
 11 concomitantly testing for acetaminophen use
 12 when assessing glutathione.
 13 Is that a reasonable
 14 expectation, if -- if the court wants to see
 15 was the scientist actually looking at the
 16 right issue here?
 17 MR. COHEN: Object to the form.
 18 A. Depending on the question, it's
 19 a reasonable desire to see data specific to
 20 acetaminophen, but I would note that the
 21 plaintiffs' experts frequently rely on
 22 studies that have nothing to do with
 23 acetaminophen.
 24 BY MR. JANUSH:
 25 Q. But you're here today, and

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1 we're here to talk about you and your work.
 2 You understand that, right?
 3 MR. COHEN: Object to the form.
 4 A. I'm here to talk about the
 5 questions that I was asked to address in my
 6 expert report.
 7 BY MR. JANUSH:
 8 Q. Uh-huh. And your work, right?
 9 MR. COHEN: Object to the form.
 10 A. I guess I'm not clear on what
 11 you mean by my work.
 12 BY MR. JANUSH:
 13 Q. Your expert report and your
 14 conclusions and your studies that you relied
 15 on is what is at issue today in front of this
 16 camera and in front of the court on this
 17 deposition, right?
 18 MR. COHEN: Object to the form.
 19 A. What is at issue today is the
 20 questions that I was asked to address in my
 21 expert report. I addressed them in the
 22 report.
 23 BY MR. JANUSH:
 24 Q. Meaning plaintiffs' experts are
 25 not in this deposition and they're not the

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1 subject of today's deposition, right?
 2 MR. COHEN: Object to the form.
 3 A. I think it's -- the -- my
 4 report is, in part, a response to the
 5 plaintiffs' experts. I think it's impossible
 6 to not cite them as a result of that or not
 7 discuss them. It's the basis of the report.
 8 BY MR. JANUSH:
 9 Q. I just want to conclude by
 10 coming back to a question I asked earlier and
 11 try and get a clean answer from you.
 12 Would you agree that in this
 13 three-page Nitsche publication, the only
 14 endpoints being addressed were -- addressed
 15 were the measurements of acetaminophen
 16 observed in the fetus and observed in the
 17 mother following administration of the 1,000
 18 milligrams of acetaminophen to the mother?
 19 MR. COHEN: I'm just going to
 20 object to the colloquy at the
 21 beginning before the question --
 22 MR. JANUSH: Fair enough.
 23 MR. COHEN: -- which implied
 24 that he didn't give a, quote, clean
 25 answer. That was improper.

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1 A. So again, what's in the study
 2 is that they -- well, their conclusion from
 3 their data -- one of their conclusions from
 4 the data is that the plasma concentrations to
 5 which a fetus or neonate -- plasma
 6 concentrations of acetaminophen -- excuse
 7 me -- after a therapeutic dose ingested by
 8 the mother to which the fetus or neonate
 9 would be exposed is no greater than that to
 10 which the mother is exposed, right?
 11 Given what we know about the
 12 lack of P4- -- lack of CYP2E1 in the brain,
 13 given what we know about the fact that there
 14 are no acetaminophen-protein adducts in the
 15 brain, even after massive overdoses of
 16 acetaminophen, given what we know about the
 17 fact that we have glutathione in the brain,
 18 including in the fetal brain, together with
 19 that information, these data suggest that
 20 acetaminophen would be safe to the fetus.
 21 Again, that's the way I take
 22 the data. I cannot comment on how the
 23 authors themselves came to their conclusions.
 24 BY MR. JANUSH:
 25 Q. But you had -- fair to say you

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1 had no problem quoting their concluding
 2 sentence and not qualifying it as being
 3 unsupported within the four corners of the
 4 actual study itself, right, in terms of the
 5 design of the study?
 6 MR. COHEN: Object to the form.
 7 A. So when we do science, you
 8 never take it in isolation, right, unless
 9 there's just nothing else ever has been done
 10 on a particular subject. You always
 11 interpret it in the context of the
 12 literature.
 13 BY MR. JANUSH:
 14 Q. Except these scientists wrote
 15 "our findings," right? They weren't looking
 16 at other literature.
 17 A. Again, they may have other
 18 studies. They may have meant our findings in
 19 terms of their results in the context of
 20 other things that they've found from other
 21 studies. I cannot comment on what they were
 22 thinking or their rationale for that
 23 statement.
 24 Q. But you felt comfortable
 25 quoting it?

<p style="text-align: right;">Page 250</p> <p>1 MR. COHEN: Objection, form.</p> <p>2 A. Yeah, I was comfortable quoting</p> <p>3 it because, again, when you take it in the</p> <p>4 context of the greater literature, it does</p> <p>5 strongly suggest that it's safe for the</p> <p>6 fetus. Or at least a neonate.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. I'm going to move on to</p> <p>9 paragraph 33, where you say: In the fetus,</p> <p>10 drugs also undergo metabolism. The human</p> <p>11 fetal liver expresses enzymes that can</p> <p>12 catalyze the sulfation of acetaminophen at</p> <p>13 levels that are comparable to the adult</p> <p>14 liver.</p> <p>15 Dr. McGill, fair to say that</p> <p>16 this publication cited at 51, Hume, regarding</p> <p>17 sulfation of thyroid hormone and dopamine</p> <p>18 during human development, that --</p> <p>19 A. I'm sorry. Footnote 51? I</p> <p>20 don't see a Hume.</p> <p>21 Q. Richard K. Hume.</p> <p>22 A. Oh. Hume is the second author.</p> <p>23 Q. Okay. So Rich -- my apologies.</p> <p>24 I read that wrong. K. Richard with R. Hume.</p> <p>25 Do you see that?</p>	<p style="text-align: right;">Page 252</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. My questions may prompt a need</p> <p>3 for you to look at it further or may not, so</p> <p>4 I'd like to ask a question, and then you tell</p> <p>5 me whether you have to look at something</p> <p>6 specifically to answer it.</p> <p>7 I appreciate that there's a</p> <p>8 conclusion or a statement on 2735 in the</p> <p>9 upper right-hand corner that says: To</p> <p>10 further our understanding of the role of</p> <p>11 sulfation of catecholamines and thyroid</p> <p>12 hormone during human development, we have</p> <p>13 studied the ontogeny of the SULT and ARS</p> <p>14 isoenzymes involved in their metabolism in</p> <p>15 key tissues, liver, lung and brain, using</p> <p>16 isoform-selective probe substrates and</p> <p>17 immunochemical techniques. Our data strongly</p> <p>18 support the idea that the human fetus has an</p> <p>19 extensive capacity for sulfation, and we</p> <p>20 demonstrate for the first time a</p> <p>21 developmentally programmed switch in the</p> <p>22 hepatic expression of the major</p> <p>23 catecholamine-metabolizing sulfotransferase,</p> <p>24 SULT1A3.</p> <p>25 Do you see that?</p>
<p style="text-align: right;">Page 251</p> <p>1 A. I do.</p> <p>2 Q. Okay. And fair to say this</p> <p>3 publication specifically concerns the role of</p> <p>4 sulfation of catecholamines and thyroid</p> <p>5 hormones during human development?</p> <p>6 A. Again, to say definitively, I</p> <p>7 would prefer to see a copy of the actual</p> <p>8 study.</p> <p>9 Q. We've marked this as 814.</p> <p>10 (Whereupon, Deposition</p> <p>11 Exhibit P814, Sulfation of Thyroid</p> <p>12 Hormone and Dopamine during Human</p> <p>13 Development: Ontogeny of Phenol</p> <p>14 Sulfotransferases and Arylsulfatase in</p> <p>15 Liver, Lung, and Brain, by Richard</p> <p>16 et al., was marked for</p> <p>17 identification.)</p> <p>18 BY MR. JANUSH:</p> <p>19 Q. And it's titled, again,</p> <p>20 Sulfation of Thyroid Hormone and Dopamine</p> <p>21 during Human Development: Ontogeny of Phenol</p> <p>22 Sulfotransferases and Arylsulfatase in Liver,</p> <p>23 Lung and Brain.</p> <p>24 (Document review.)</p> <p>25 ///</p>	<p style="text-align: right;">Page 253</p> <p>1 A. Yes.</p> <p>2 Q. In this study, weren't tissues</p> <p>3 obtained from postmortem within 12 hours of</p> <p>4 certification of death?</p> <p>5 A. I'd have to double-check the</p> <p>6 methods.</p> <p>7 Q. Please do.</p> <p>8 (Document review.)</p> <p>9 A. So it states: Tissue was</p> <p>10 obtained from fetuses within six hours</p> <p>11 following termination of pregnancy. Infant</p> <p>12 tissue was obtained at routine postmortem</p> <p>13 within 12 hours of certification of death.</p> <p>14 BY MR. JANUSH:</p> <p>15 Q. Okay. Did any aspect of this</p> <p>16 study address the relevance between APAP</p> <p>17 sulfation or acetaminophen sulfation and</p> <p>18 sulfation of iodothyronines or thyroxine T4,</p> <p>19 a prohormone secreted by the thyroid?</p> <p>20 A. I'm sorry, can you ask the</p> <p>21 question again? I want to make sure I</p> <p>22 understand.</p> <p>23 Q. Yeah.</p> <p>24 Did any aspect of this study</p> <p>25 address the relationship between</p>

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1 acetaminophen sulfation and sulfation of
 2 thyroxine T4?

3 A. Right. So they actually look
 4 at multiple sulfation substrates, right? One
 5 of those -- let's see if I can find it again
 6 here.

7 So -- so -- I'm sorry, on the
 8 first page, 2734, the right-hand column,
 9 close to the top -- I think it's the second
 10 sentence. They state: Human SULT enzymes
 11 can be subdivided, based on amino acid
 12 sequence identity and enzymatic function,
 13 into phenol SULT, SULT1, and steroid SULT,
 14 SULT2, families, where the SULT1 family
 15 comprises enzymes metabolizing phenolic
 16 xenobiotics and iodothyronines and
 17 catecholamines.

18 So you can see there that they
 19 are pointing out that they're interested in
 20 SULT1A family, correct? Acetaminophen is
 21 metabolized by members of the SULT1A family
 22 of sulfotransferases.

23 In addition, one of the
 24 substrates that they use -- they don't just
 25 use the substrates that you mentioned. For

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1 example, just one example, they also look at
 2 sulfation of 4-nitrophenol, which they seem
 3 to use as a marker of SULT1A1. And again,
 4 SULT1A, sulfotransferases are involved in
 5 acetaminophen metabolism.

6 And if I can find that one
 7 statement again.

8 (Document review.)

9 BY MR. JANUSH:

10 Q. What I'm addressing, though,
 11 is: Did this study actually review
 12 acetaminophen?

13 A. I don't recall if they
 14 specifically mentioned acetaminophen in this
 15 paper or not.

16 Q. Why don't you look through it.

17 A. You --

18 Q. You had a few minutes before to
 19 look through it.

20 A. You'd like me to read the
 21 entire paper?

22 Q. Well, just -- you can just scan
 23 it. I want to confirm whether you cited a
 24 paper that has nothing to do with
 25 acetaminophen.

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1 A. Well --

2 Q. I get what you're saying about
 3 SULT1 and all that, but I'm addressing
 4 whether acetaminophen sulfation was tested in
 5 this paper.

6 A. I don't believe they
 7 specifically looked at acetaminophen
 8 sulfation. Again, however, this is standard
 9 practice in the field, right? You use
 10 well-characterized substrates to look at
 11 enzyme activity, and especially
 12 drug-metabolizing enzyme activity.

13 And so again, acetaminophen is
 14 known to be sulfated by members of the SULT1A
 15 family, and they have shown SULT1A activity
 16 here.

17 Q. But not shown acetaminophen in
 18 this entire study, right?

19 A. Not specifically, but the
 20 results are suggestive that there is
 21 acetaminophen sulfation.

22 Q. Well, SULT1 sulfation is
 23 broader than acetaminophen sulfation, isn't
 24 it?

25 A. True.

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1 Q. Yeah. How much broader?

2 A. I -- I mean, I'm not sure how
 3 to answer that question.

4 Q. Well, what does SULT1 sulfation
 5 entail beyond acetaminophen sulfation?

6 A. I'm sure it sulfates other
 7 drugs and some other chemicals as well.

8 Q. So what led you to speculate
 9 that you're sure that acetaminophen was
 10 relevant here?

11 MR. COHEN: Object to the form.

12 A. Let me find. So I -- let me --
 13 which part -- I'm sorry, can you remind me
 14 what -- which part of the expert report
 15 you're referring to? Oh, I see it. I'm
 16 sorry. Paragraph 33.

17 BY MR. JANUSH:

18 Q. 33.

19 A. So they express enzymes that
 20 are -- that can or, in other words, are
 21 capable of sulfation of acetaminophen, and
 22 that's what they've shown here. These are
 23 enzymes -- they're testing enzymes that
 24 are -- that can sulfate acetaminophen.

25 In addition to that, I have

<p style="text-align: right;">Page 258</p> <p>1 additional references in that footnote, one 2 of which, at least, does specifically address 3 acetaminophen. 4 Q. Let's turn to paragraph 34 on 5 page 26. And here you're addressing the 6 blood-brain barrier. 7 Dr. McGill, as part of your 8 report in this case, are you opining that 9 acetaminophen does not cross the fetal 10 blood-brain barrier? 11 A. No. 12 Q. Okay. You don't know what 13 amount of acetaminophen is getting into the 14 fetal brain at various stages of pregnancy, 15 right? 16 A. At various stages of pregnancy? 17 I don't recall specifically if any of the 18 studies I cited looked at that, getting into 19 the fetal brain at various stages of 20 pregnancy. 21 Again -- well, the short answer 22 is no, but we do know how much is in the 23 fetal plasma, and it can't be more than that. 24 And the amount in the fetal 25 plasma, by the way, one example of that comes</p>	<p style="text-align: right;">Page 260</p> <p>1 humans, maximum acetaminophen concentrations 2 were far lower in the brain extracellular 3 fluid than in plasma in these animals. These 4 data show that the blood-brain barrier delays 5 entry of acetaminophen into the brain, 6 keeping peak concentrations lower in the 7 brain than in plasma. 8 Although these studies were 9 performed in adult humans and animals, it has 10 been demonstrated that the blood-brain 11 barrier is intact in the human embryo/fetus 12 by approximately 8 weeks of gestation, and 13 functional by 10 to 12 weeks. 14 Then you have a comma and a 15 footnote, 56 -- indicating that the fetal 16 brain is also protected. And you have 17 footnote 57. And we're going to go through 18 each footnote 56 and 57. 19 But before I do that, I'll just 20 address initially: 21 You cited literature at 22 footnote 56 by Kate Goasdoué, Stephanie 23 Miller, Paul Colditz and Tracey Björkman, a 24 Review: The blood-brain barrier, protecting 25 the developing fetal brain.</p>
<p style="text-align: right;">Page 259</p> <p>1 from the study that we were discussing a 2 moment ago, looking at that neonatal 3 exposure, and they showed that the 4 concentrations and the -- well, at least the 5 neonatal samples and the cord blood samples 6 were the same as in the mother, 7 concentrations of acetaminophen. 8 And again, because 9 acetaminophen is a weak acid, a pKa of about 10 9.5, it's uncharged and not very polar at 11 physiological pH, which means it can cross in 12 brains fairly freely. There's a delay with 13 the blood-brain barrier, but it can cross. 14 And so there's no reason to believe that it 15 would accumulate in the brain, and so -- 16 including the fetal brain. 17 And so we can assume that 18 whatever concentration is in the fetal brain 19 at any stage of fetal or embryonic 20 development, it's no greater than what's in 21 the plasma. 22 Q. I want to focus on some 23 particular statements you make in this 24 paragraph. 25 Similar to the results in</p>	<p style="text-align: right;">Page 261</p> <p>1 Do you recall if there's 2 anything about acetaminophen in this review? 3 A. Off the top of my head, I do 4 not recall. 5 Q. Okay. Would it surprise you if 6 there was nothing about acetaminophen in this 7 review? 8 MR. COHEN: Objection, form. 9 A. No, because I'm not citing this 10 review as evidence for whether or not 11 acetaminophen crosses the blood-brain 12 barrier. I'm just citing it as a source for 13 the statement that the blood-brain barrier is 14 intact by 10 to 12 weeks' gestation. 15 This citation was not intended 16 to say anything about acetaminophen. 17 BY MR. JANUSH: 18 Q. Did you misrepresent what 19 Goasdoué et al. actually said in their 20 publication? 21 MR. COHEN: Objection, form. 22 A. I don't believe so. 23 BY MR. JANUSH: 24 Q. Let's walk through it. 25 THE STENOGRAPHER: Is this a</p>

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1 new exhibit?

2 MR. JANUSH: This is exhibit

3 P815.

4 (Whereupon, Deposition

5 Exhibit P815, Review: The blood-brain

6 barrier; protecting the developing

7 fetal brain, by Goasdoué et al., was

8 marked for identification.)

9 BY MR. JANUSH:

10 Q. We're going to go to Section 8,

11 Conclusion. We're going to blow this up.

12 I'm going to read it.

13 Despite the presence of

14 placental efflux transporters, the placenta

15 is an imperfect drug barrier. Given

16 sufficient time and dosage, most drugs can

17 breach the placenta and enter the fetal

18 circulation, posing a teratogenic risk to the

19 fetal brain.

20 Let me stop there for a second.

21 Is a teratogenic risk to the fetal brain a

22 good thing or a bad thing?

23 MR. COHEN: Object to the form.

24 A. A risk is a risk. It doesn't

25 mean that something happens, for starters.

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1 Second of all, my statement is

2 about the blood-brain barrier. This is about

3 the placental barrier. They mention the

4 brain, but they're not discussing that in

5 this sentence.

6 BY MR. JANUSH:

7 Q. I'm not done. I have a lot

8 more to go.

9 Although the placenta and

10 blood-brain barrier have several efflux

11 transporters in common, the blood-brain

12 barrier is a far more structurally complex

13 and restrictive system. To cross the

14 blood-brain barrier and enter the central

15 nervous system, drugs need to be small and

16 lipophilic or have dedicated transport

17 systems.

18 Drugs with these properties

19 would easily cross the placental barrier even

20 with functional efflux transporters, as quick

21 diffusion surpasses the ability of efflux

22 transporters to pump substances from the

23 fetal circulation. Understanding how the

24 blood-brain barrier functions during

25 development of the fetus is essential to

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1 ensuring optimal brain growth and protection

2 from drugs and toxins once they cross the

3 placenta.

4 Given the differences in

5 blood-brain development -- blood-brain

6 barrier development across species,

7 refinement of animal models is critical

8 before application to the human.

9 So far I've read that

10 correctly, right?

11 A. Yes. As far as I've been able

12 to keep up, yeah.

13 Q. Well, please stay with me and

14 let me know if I'm losing you because the

15 next sentences are really critical to this

16 case and to this article.

17 Minimizing drug exposure in the

18 fetus is vital to reducing teratogenic

19 effects and long-term neurological disease.

20 You ignored that statement when

21 you cited to Goasdoué, right?

22 A. No. Again, I cited this

23 article as support for my statement that the

24 blood-brain barrier is intact by 10 to

25 12 weeks' gestation. I didn't make any

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1 comments in referencing that article about

2 teratogenicity, drug exposure. I just said

3 the blood-brain barrier was intact.

4 Q. Okay. That's actually, by the

5 way, not so true either, right? A -- by

6 8 weeks of gestation and functional by 10-12

7 weeks -- 10 to 12 weeks -- is your statement

8 in your report in terms of the timeline for a

9 blood-brain barrier to be intact.

10 But isn't it scientifically

11 established that the blood-brain barrier

12 continues forming and becoming tighter

13 throughout gestation and even continues to

14 develop postnatally?

15 A. I'm not an expert on

16 blood-brain barrier development. I'm just

17 citing what I found in those two articles.

18 Furthermore --

19 Q. But this case --

20 A. Sorry. Go ahead.

21 Q. This case is --

22 MR. COHEN: I'm sorry, were you

23 finished?

24 MR. JANUSH: Yeah.

25 A. Yeah, furthermore, I don't

<p>Page 266</p> <p>1 dispute anywhere in my report that</p> <p>2 acetaminophen crosses the blood-brain</p> <p>3 barrier. I guess I don't -- I don't dispute</p> <p>4 that.</p> <p>5 BY MR. JANUSH:</p> <p>6 Q. Do you agree that it crosses</p> <p>7 the blood-brain barrier and can cause</p> <p>8 teratogenic effects to the fetus?</p> <p>9 MR. COHEN: Objection, form.</p> <p>10 A. That acetaminophen can cross</p> <p>11 the blood-brain barrier and cause teratogenic</p> <p>12 effects? I mean, I've seen no data that</p> <p>13 indicates that. No reliable, reproducible,</p> <p>14 scientifically rigorous data that indicates</p> <p>15 that.</p> <p>16 BY MR. JANUSH:</p> <p>17 Q. And again, you haven't produced</p> <p>18 your methodology concerning your searches and</p> <p>19 how you arrived at the literature you</p> <p>20 selected to review for your report, right?</p> <p>21 MR. COHEN: Objection, form.</p> <p>22 A. I think I explained my</p> <p>23 methodology pretty clearly this morning.</p> <p>24 Again, I used the scientific method. I'm</p> <p>25 happy to --</p>	<p>Page 268</p> <p>1 blood-brain barrier is -- based on the</p> <p>2 references that I cited, is intact during</p> <p>3 certain -- by a certain point in the</p> <p>4 embryonic or fetal development.</p> <p>5 I also discussed acetaminophen</p> <p>6 pharmacokinetics in the CSF. In order to get</p> <p>7 to the CSF, it must cross the blood-brain</p> <p>8 barrier. And I am an expert in acetaminophen</p> <p>9 metabolism and pharmacokinetics, so I can</p> <p>10 address that.</p> <p>11 I'm not an expert in</p> <p>12 blood-brain barrier development or this</p> <p>13 specific question about maternal environment.</p> <p>14 That's not my expertise.</p> <p>15 Q. Okay. And now I promised we'd</p> <p>16 get to the next footnote. I've only</p> <p>17 addressed Goasdoué at 56, after you say:</p> <p>18 Although these studies were performed in</p> <p>19 adult humans and animals, it has been</p> <p>20 demonstrated that the blood-brain barrier is</p> <p>21 intact in the human embryo and fetus by</p> <p>22 approximately 8 weeks of gestation and fully</p> <p>23 functional by 10 to 12 weeks.</p> <p>24 You address, quote: indicating</p> <p>25 that the fetal brain is also protected.</p>
<p>Page 267</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. No, we're not doing that again.</p> <p>3 MR. COHEN: Well, let the</p> <p>4 record reflect you asked and you cut</p> <p>5 him off.</p> <p>6 BY MR. JANUSH:</p> <p>7 Q. And let's go to the next</p> <p>8 paragraph: A significant clinical challenge</p> <p>9 is the protection of the vulnerable fetal</p> <p>10 brain from drugs in the maternal environment.</p> <p>11 The changes in placental or blood-brain</p> <p>12 barrier function due to drug exposure from</p> <p>13 the maternal environment have significant</p> <p>14 clinical relevance as the functional outcomes</p> <p>15 vary and are often unknown.</p> <p>16 As you sit here today, do you</p> <p>17 agree with this statement?</p> <p>18 A. Again, I'm -- I'm not an expert</p> <p>19 on blood-brain barrier development, and this</p> <p>20 is not what I study, so I -- I really -- I</p> <p>21 can't comment.</p> <p>22 Q. But you included a section in</p> <p>23 your report specifically addressing the</p> <p>24 blood-brain barrier, right?</p> <p>25 A. I mentioned that the</p>	<p>Page 269</p> <p>1 That's -- that's a statement,</p> <p>2 right? You're indicating -- are you</p> <p>3 indicating -- you are -- let me -- let me ask</p> <p>4 this question differently.</p> <p>5 Is this your work or someone</p> <p>6 who wrote this for you?</p> <p>7 MR. COHEN: No, no, no, no.</p> <p>8 Stop.</p> <p>9 A. I wrote the report.</p> <p>10 MR. COHEN: Stop. Stop.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. You wrote the report.</p> <p>13 MR. JANUSH: So no, I'm --</p> <p>14 MR. COHEN: I know you didn't</p> <p>15 do it intentionally, but you said</p> <p>16 "fully functional" and the word</p> <p>17 "fully" is not there.</p> <p>18 MR. JANUSH: I did not mean</p> <p>19 that. You are correct. Thank you.</p> <p>20 MR. COHEN: Thank you.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. So you are, in the first</p> <p>23 portion of this sentence preceding the comma,</p> <p>24 addressing that the blood-brain barrier has</p> <p>25 been demonstrated to be intact by</p>

<p style="text-align: right;">Page 270</p> <p>1 approximately 8 weeks of gestation and fully 2 functional by 10 to 12 weeks. 3 MR. COHEN: No. 4 BY MR. JANUSH: 5 Q. And then concluding, indicating 6 that the fetal brain is also protected, cite 7 footnote 57, Bell/O'Shaughnessy publication. 8 MR. COHEN: Object to the form. 9 Go ahead and answer, but he 10 didn't mean fully. 11 MR. JANUSH: Oh, sorry. I said 12 it again? 13 MR. COHEN: Yes. 14 MR. JANUSH: We'll delete 15 "fully" from the record. 16 MR. COHEN: It's fine. 17 MR. JANUSH: "Functional" is 18 what I meant. You are correct. 19 BY MR. JANUSH: 20 Q. Okay. So my question is: Did 21 you actually read the citation at 22 footnote 57? Did you read that, that piece 23 of literature? 24 A. Yes. 25 Q. You did?</p>	<p style="text-align: right;">Page 272</p> <p>1 established through a body of literature 2 describing rigorous, reproducible scientific 3 studies. 4 Q. So I'm going to give you a 5 different definition and see if you agree. 6 Would you agree that biological 7 plausibility concerns whether the 8 hypothesized causal link is credible in light 9 of what is known from science and medicine 10 about the human body and the potentially 11 offending agent? 12 A. I dislike the term "causal 13 link," and I -- I would qualify -- so I 14 would -- I would say that there has to be a 15 firm mechanistic link, as I said, a 16 well-established mechanism. 17 And in terms of how we define 18 credible, again, that's referring to my 19 statement of -- or I would say that that's 20 related to what I said about needing to have 21 studies that are rigorous and reproducible. 22 Q. You cited a publication at 23 footnote 57 for the concept that the fetal 24 brain is protected by the blood-brain 25 barrier, right?</p>
<p style="text-align: right;">Page 271</p> <p>1 A. Uh-huh. 2 Q. Do you remember it? 3 A. I mean, it's been a little 4 while since I looked at it. I don't recall 5 every detail off the top of my head. 6 Q. Do you remember what was being 7 studied in this piece of literature called 8 The development and function of the brain 9 barriers - an overlooked consideration for 10 chemical toxicity? 11 A. If my recollection is correct, 12 it was a review. I don't think it was a 13 study. 14 Q. Do you know what contaminants 15 were being reviewed? 16 A. Off the top of my head, I don't 17 recall. 18 Q. What does "biological 19 plausibility" mean? 20 A. So when something -- in order 21 for something to be biologically plausible, 22 at least, you know, my definition, in order 23 for something to be biological plausible -- 24 biologically plausible, excuse me -- you have 25 to have a firm mechanism that has been</p>	<p style="text-align: right;">Page 273</p> <p>1 A. First of all, when I say 2 protected here, I'm not saying that it 3 prevents acetaminophen from crossing the 4 blood-brain barrier, right? Actually, in 5 other parts of this paragraph, I state that 6 if you look at overall exposure, the AUC, 7 there's a one-to-one relationship between 8 plasma and CSF, which means that the 9 acetaminophen gets in there, right? It just 10 has delayed entry. And that's what the 11 studies I've cited in rodents and humans 12 show. 13 So I want to be careful about 14 how we're using the word "protected." 15 In addition to that -- so 16 you're asking me that's what I've cited 17 to show that? 18 BY MR. JANUSH: 19 Q. You cited this article, this -- 20 A. Right. 21 Q. -- specific publication to 22 demonstrate that it indicates that the fetal 23 brain is also protected, right? 24 A. Yeah, from people who have 25 reviewed the literature on that -- the</p>

<p style="text-align: right;">Page 274</p> <p>1 relevant literature on that topic.</p> <p>2 Q. Okay. So let's -- let me show</p> <p>3 you what you considered the relevant</p> <p>4 literature on this topic. It's P816.</p> <p>5 (Whereupon, Deposition</p> <p>6 Exhibit P816, The development and</p> <p>7 function of the brain barriers -- an</p> <p>8 overlooked consideration for chemical</p> <p>9 toxicity, by Bell et al., was marked</p> <p>10 for identification.)</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. The development and function of</p> <p>13 the brain barriers - an overlooked</p> <p>14 consideration for chemical toxicity.</p> <p>15 I'm going to just ask you a</p> <p>16 simple question at the outset: Can you</p> <p>17 identify what contaminants -- what two</p> <p>18 contaminants were being addressed in this</p> <p>19 entire study as it concerns the blood-brain</p> <p>20 barrier? And I think it's in the closing</p> <p>21 remarks at page 19.</p> <p>22 A. So without reading through it</p> <p>23 again, I would not be comfortable saying for</p> <p>24 sure what two. I can tell you two that I see</p> <p>25 right away.</p>	<p style="text-align: right;">Page 276</p> <p>1 and find me where acetaminophen is addressed</p> <p>2 anywhere within this piece of literature</p> <p>3 addressing the protection of blood-brain</p> <p>4 barriers.</p> <p>5 MR. COHEN: That's a different</p> <p>6 question. So ask that question.</p> <p>7 MR. JANUSH: I did.</p> <p>8 A. If you would like to do that,</p> <p>9 we can do that.</p> <p>10 BY MR. JANUSH:</p> <p>11 Q. I'd like for you to find</p> <p>12 where -- find me where acetaminophen is</p> <p>13 addressed in this report, unless you know the</p> <p>14 answer --</p> <p>15 A. But I --</p> <p>16 I'm sorry, I interrupted you.</p> <p>17 I'm sorry.</p> <p>18 Q. Unless you know the answer</p> <p>19 already and you know that this is a bisphenol</p> <p>20 and PFAS study only, which I think you know.</p> <p>21 A. Okay. A couple of things.</p> <p>22 First of all, it's not -- this is not a</p> <p>23 study, right? It's a review of the</p> <p>24 literature that cites multiple other studies.</p> <p>25 In addition to that, I don't</p>
<p style="text-align: right;">Page 275</p> <p>1 Q. PFAS and bisphenol, right?</p> <p>2 A. Those are the two that I see</p> <p>3 right away. I can't say if there are any</p> <p>4 others. I'll have to take your word for it.</p> <p>5 Q. Well, I'll make you a deal so</p> <p>6 we don't take up a lot of time. You get a</p> <p>7 chance to issue an errata if PFAS and</p> <p>8 bisphenols are not the only two chemicals</p> <p>9 being studied in this -- in this piece of</p> <p>10 literature for purposes of analyzing the</p> <p>11 blood-brain barrier.</p> <p>12 MR. COHEN: We're not making</p> <p>13 deals. Sorry, just ask your</p> <p>14 questions.</p> <p>15 MR. JANUSH: Then I can go off</p> <p>16 the record and have him review it on</p> <p>17 his time and tell me if PFAS and</p> <p>18 bisphenol are the only two.</p> <p>19 MR. COHEN: No --</p> <p>20 MR. JANUSH: Actually, you know</p> <p>21 what? I'm going to make him do this</p> <p>22 on video because I think this is going</p> <p>23 to be painful.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. So let's go through the report,</p>	<p style="text-align: right;">Page 277</p> <p>1 see the relevance because I have not disputed</p> <p>2 that acetaminophen crosses the blood-brain</p> <p>3 barrier. In fact, I've said that it does,</p> <p>4 and I've cited data showing that it does in</p> <p>5 my report.</p> <p>6 When I've used the word</p> <p>7 "protected," as I stated just a moment ago,</p> <p>8 we need to be careful how we're using it.</p> <p>9 Perhaps I used it a little inartfully in that</p> <p>10 sentence. When I used that word, what I was</p> <p>11 referring to was the delay in entry of</p> <p>12 acetaminophen to the CSF, and therefore, the</p> <p>13 brain compartment.</p> <p>14 Q. But, Doctor --</p> <p>15 A. What that delay -- if I may</p> <p>16 finish.</p> <p>17 Q. Yeah. I didn't mean to</p> <p>18 interrupt there.</p> <p>19 A. What that delay means is that</p> <p>20 the maximum peak concentrations achieved in</p> <p>21 the CSF are lower even than the plasma</p> <p>22 concentrations, the maximum peak plasma</p> <p>23 concentrations.</p> <p>24 So what that means is that at</p> <p>25 one point in time, the brain is always -- or,</p>

<p style="text-align: right;">Page 278</p> <p>1 generally speaking, exposed to less than the</p> <p>2 rest of the body.</p> <p>3 Q. Are you --</p> <p>4 A. So -- I'm sorry. Go ahead.</p> <p>5 Q. Are you aware that bisphenol is</p> <p>6 about 100 grams per mole heavier and larger</p> <p>7 than acetaminophen?</p> <p>8 A. I don't know all the chemical</p> <p>9 properties of -- first of all, there are</p> <p>10 multiple bisphenols, right? There's not just</p> <p>11 one. I don't know all the chemical</p> <p>12 properties of all of them.</p> <p>13 Q. Are you aware that PFAS is</p> <p>14 about three times larger than acetaminophen,</p> <p>15 from a molecular size and weight?</p> <p>16 A. Once again, PFAS stands for</p> <p>17 perfluorinated alkylated substances. This is</p> <p>18 a large group of chemicals that have multiple</p> <p>19 different properties. I don't know the</p> <p>20 characteristics of every single one of them.</p> <p>21 Q. If you looked at toxicants in</p> <p>22 this report that are two and three times</p> <p>23 larger than acetaminophen to conclude that</p> <p>24 acetaminophen -- that the fetal brain is also</p> <p>25 protected from acetaminophen, that would be a</p>	<p style="text-align: right;">Page 280</p> <p>1 MR. COHEN: Do you need to take</p> <p>2 a break?</p> <p>3 THE WITNESS: I can finish my</p> <p>4 answer.</p> <p>5 MR. COHEN: Yeah, finish your</p> <p>6 answer. We've been going over an hour</p> <p>7 anyway, so...</p> <p>8 THE WITNESS: Okay.</p> <p>9 A. So, I'm sorry, let me -- so</p> <p>10 when I use the term "protected," I'm</p> <p>11 referring to the delay of entry into the</p> <p>12 brain across the blood-brain barrier. That</p> <p>13 is demonstrated in the two studies that I</p> <p>14 cited above, the human study as well as the</p> <p>15 rat study.</p> <p>16 Because again, when you look at</p> <p>17 the data in those studies -- which I'm</p> <p>18 happy -- if you want to produce the paper,</p> <p>19 I'll show it to you. They see that the</p> <p>20 acetaminophen enters there a bit more slowly,</p> <p>21 and that's why the peak CSF concentrations of</p> <p>22 acetaminophen are roughly half or less than</p> <p>23 the peak plasma concentrations of</p> <p>24 acetaminophen at therapeutic doses.</p> <p>25 So again, that's what I mean</p>
<p style="text-align: right;">Page 279</p> <p>1 bad thing, right?</p> <p>2 MR. COHEN: Objection, form.</p> <p>3 A. Again, I did not dispute that</p> <p>4 acetaminophen crosses the blood-brain</p> <p>5 barrier. In fact, I said that it does.</p> <p>6 BY MR. JANUSH:</p> <p>7 Q. But you said that the fetal</p> <p>8 brain is protected, right?</p> <p>9 MR. COHEN: I don't think he</p> <p>10 was finished.</p> <p>11 MR. JANUSH: Sorry.</p> <p>12 A. What -- again, what I meant by</p> <p>13 the word "protected" is that there is a delay</p> <p>14 in entry through the blood-brain barrier, and</p> <p>15 that is not just me claiming that. This is</p> <p>16 not the study that shows that.</p> <p>17 This is a study in which, if</p> <p>18 memory serves correctly, they just mentioned</p> <p>19 that the blood-brain barrier might protect</p> <p>20 against some chemicals, right? The studies</p> <p>21 that show the delay in entry are --</p> <p>22 (Telephonic interruption.)</p> <p>23 THE WITNESS: I'm so sorry. I</p> <p>24 meant to silence my phone. I</p> <p>25 apologize for that.</p>	<p style="text-align: right;">Page 281</p> <p>1 when I use the term "protected." I'm not</p> <p>2 saying acetaminophen doesn't cross the</p> <p>3 blood-brain barrier.</p> <p>4 BY MR. JANUSH:</p> <p>5 Q. Dr. McGill, when you're saying</p> <p>6 in your report that the blood-brain barrier</p> <p>7 is intact in the human embryo/fetus by</p> <p>8 approximately 8 weeks of gestation and</p> <p>9 functional by 10 to 12 weeks, indicating that</p> <p>10 the fetal brain is protected, you've cited</p> <p>11 for the protective component of that sentence</p> <p>12 the Kiersten Bell publication we're going</p> <p>13 over, right, this PFAS and bisphenol</p> <p>14 publication? That's all I'm addressing.</p> <p>15 A. So you have to take it in the</p> <p>16 context of the data above, right? Again, as</p> <p>17 a scientist, you don't interpret data in --</p> <p>18 or don't interpret statements or data in</p> <p>19 isolation.</p> <p>20 The studies above show that in</p> <p>21 adult humans and in rats, there's delayed</p> <p>22 entry of acetaminophen across the blood-brain</p> <p>23 barrier, which reduces the maximum CSF</p> <p>24 concentration that's achieved.</p> <p>25 We don't have specifically data</p>

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1 for crossing the blood-brain barrier in the
 2 embryo or fetus. In the absence of that
 3 data, all we can really do is say, okay,
 4 well, might this happen in an embryo or
 5 fetus? Well, if they have a blood-brain
 6 barrier intact, then it might happen.
 7 So that's -- those are the
 8 statements that I'm making in this part, and
 9 that's what the citations support.
 10 Q. How --
 11 A. The data showing the delayed
 12 entry are in the citations above that.
 13 Q. If Judge Cote were reading your
 14 report, how would she know all of that extra
 15 explanation of what you meant based on the
 16 words you actually did include here?
 17 MR. COHEN: Objection to the
 18 form.
 19 A. Again, I have cited these data
 20 above.
 21 BY MR. JANUSH:
 22 Q. Yeah. But, Dr. McGill --
 23 A. I --
 24 Q. -- holding it up --
 25 A. I think it's clear, and --

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1 MR. COHEN: Let him finish.
 2 A. -- maybe there can be a matter
 3 of disagreement over my writing style. I
 4 felt it was clear.
 5 BY MR. JANUSH:
 6 Q. I understand that you felt it
 7 was clear, but you -- you footnoted that the
 8 fetal brain is also protected by citing to a
 9 PFAS and bisphenol study where both of those
 10 toxicants are significantly larger than
 11 acetaminophen.
 12 And so I'm asking you whether
 13 that was an intellectually honest scientific
 14 conclusion.
 15 MR. COHEN: Object to the form.
 16 A. Yes, when you understand the
 17 way that I defined "protected" and that this
 18 is -- statement is based on terms of data on
 19 the studies that I cited and described above.
 20 When you interpret it in the context of the
 21 report, yes, this is absolutely an accurate
 22 statement.
 23 BY MR. JANUSH:
 24 Q. Okay. You also --
 25 MR. COHEN: So --

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1 MR. JANUSH: Just one more
 2 question.
 3 MR. COHEN: Yeah, yeah.
 4 BY MR. JANUSH:
 5 Q. You also -- but you appreciate,
 6 do you not, that the size -- the size of the
 7 molecule has everything to do with what
 8 passes through the blood-brain barrier, how
 9 quickly, how easily, and at what particular
 10 point of gestation, right?
 11 A. So again, the size is one
 12 factor. There's also the actual chemical
 13 properties of the drug. As I described --
 14 and again, I'm not disputing that
 15 acetaminophen crosses the blood-brain
 16 barrier.
 17 Acetaminophen is much smaller,
 18 yeah. It's at physiological pH, around 7.4.
 19 It's a weak acid with pKa 9.5, so it's
 20 uncharged at physiological pH, and it's
 21 lipophilic enough that it crosses the
 22 blood-brain barrier. I have not disputed
 23 that.
 24 Q. So what was the protection that
 25 you were citing to at footnote 57?

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1 A. Excuse me, I'm sorry, I didn't
 2 mean to interrupt.
 3 As I've stated multiple times
 4 now, when I said "protected," I'm referring
 5 to the delay in entry to the blood-brain
 6 barrier. We have empirical evidence for
 7 that. That's shown in the two studies that I
 8 cited above, above these statements.
 9 MR. COHEN: Good time for a
 10 break?
 11 MR. JANUSH: Sure.
 12 MR. COHEN: Thank you.
 13 THE VIDEOGRAPHER: We are going
 14 off record. The time is 3:01.
 15 (Recess taken, 3:01 p.m. to
 16 3:23 p.m. CDT)
 17 THE VIDEOGRAPHER: We're going
 18 back on record. The time is 3:23.
 19 BY MR. JANUSH:
 20 Q. Dr. McGill, one of the key
 21 opinions in your report concerns the excess
 22 NAPQI hypothesis; is that correct?
 23 A. I discuss the excess NAPQI
 24 hypothesis.
 25 Q. Is it not one of the key

<p style="text-align: right;">Page 286</p> <p>1 opinions in your report?</p> <p>2 A. I haven't heard an opinion in</p> <p>3 the question.</p> <p>4 Q. The opinion you offer on the</p> <p>5 excess NAPQI hypothesis is -- sorry, I'll ask</p> <p>6 it differently. I'll ask it differently.</p> <p>7 At paragraph 39, you address:</p> <p>8 The liver contains a large amount of CYP2E1</p> <p>9 enzyme that can generate NAPQI, and it</p> <p>10 encounters more acetaminophen than other</p> <p>11 organs due to first-pass metabolism. Yet,</p> <p>12 because of the presence of glutathione, an</p> <p>13 overdose of acetaminophen of around at least</p> <p>14 10 grams in a single dose is required to</p> <p>15 cause clinically significant liver injury.</p> <p>16 Therefore, to establish the biological</p> <p>17 plausibility of plaintiffs' experts'</p> <p>18 hypothesis that maternal ingestion of</p> <p>19 recommended dose, maximum of 1 gram, of</p> <p>20 acetaminophen causes developmental</p> <p>21 neurotoxicity through NAPQI expression in the</p> <p>22 embryonic/fetal brain, it must be</p> <p>23 demonstrated that, (a) CYP2E1 enzyme is</p> <p>24 present in the embryonic/fetal brain at</p> <p>25 levels that are at least comparable to the</p>	<p style="text-align: right;">Page 288</p> <p>1 liver?</p> <p>2 A. It's extremely well established</p> <p>3 through many, many studies over the last</p> <p>4 50 years that you have to have an overdose of</p> <p>5 acetaminophen to have clinically significant</p> <p>6 liver -- liver entry, right?</p> <p>7 The liver has a lot of P450,</p> <p>8 and so in order for -- so we know, right,</p> <p>9 that an organ with a lot of P450 requires</p> <p>10 this overdose, roughly an overdose in this</p> <p>11 range of 10 grams in a single dose, in order</p> <p>12 to develop toxicity. So --</p> <p>13 Q. So -- okay. Sorry.</p> <p>14 A. So certainly you wouldn't</p> <p>15 expect toxicity in another organ that doesn't</p> <p>16 have as much CYP2E1, certainly not at</p> <p>17 therapeutic doses.</p> <p>18 Q. Can you point me to a piece of</p> <p>19 scientific literature saying that a baby in</p> <p>20 utero needs -- a fetus in utero needs at</p> <p>21 least comparable levels of CYP2E1 enzyme in</p> <p>22 the brain as they would have in the liver?</p> <p>23 A. Again, therapeutic doses don't</p> <p>24 cause toxicity in the liver. Only overdoses</p> <p>25 do. The liver has an enormous amount of</p>
<p style="text-align: right;">Page 287</p> <p>1 liver, and (b) embryonic/fetal brain</p> <p>2 glutathione concentration is insufficient to</p> <p>3 detoxify any NAPQI that may be produced.</p> <p>4 Is that one of the key opinions</p> <p>5 you offer in your report?</p> <p>6 MR. COHEN: Objection, form.</p> <p>7 A. It is -- how to say that. It's</p> <p>8 not a conclusion. It is what you would have</p> <p>9 to show in my opinion to demonstrate -- I</p> <p>10 mean, to do what I've written here.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. Yeah, I understand that you</p> <p>13 didn't address yet what's been demonstrated,</p> <p>14 but those are -- those two functions, (a) and</p> <p>15 (b) of paragraph 39, you believe plaintiffs</p> <p>16 must demonstrate; is that right?</p> <p>17 A. Yes.</p> <p>18 Q. What published literature do</p> <p>19 you rely on for the proposition that to</p> <p>20 establish maternal ingestion at recommended</p> <p>21 doses causes neurotoxicity through NAPQI</p> <p>22 expression in the embryonic/fetal brain it</p> <p>23 must be demonstrated that CYP2E1 enzyme is</p> <p>24 present in the embryonic/fetal brain at</p> <p>25 levels that are at least comparable to the</p>	<p style="text-align: right;">Page 289</p> <p>1 CYP2E1. If you had any less CYP2E1, well, if</p> <p>2 you don't get injury at therapeutic doses in</p> <p>3 the liver and you have even less CYP2E1, then</p> <p>4 you're not going to get injury in that organ</p> <p>5 with less CYP2E1.</p> <p>6 Q. I'm going to ask it again.</p> <p>7 Can you point me to any</p> <p>8 literature that supports the opinion that</p> <p>9 plaintiffs must demonstrate that CYP2E1</p> <p>10 enzyme is present in the embryonic/fetal</p> <p>11 brains at levels that are at least comparable</p> <p>12 to the liver?</p> <p>13 A. Sorry, I think your question</p> <p>14 is -- you're asking me if there are -- can I</p> <p>15 point you to literature that shows there are</p> <p>16 comparable levels of CYP2E1 in the brain to</p> <p>17 the liver? Sounds like that was your</p> <p>18 question this time.</p> <p>19 Q. You're saying --</p> <p>20 A. There are no --</p> <p>21 Q. -- for us to establish</p> <p>22 biological plausibility, can you establish --</p> <p>23 can you point me to any literature that</p> <p>24 supports that we would need to show that</p> <p>25 plaintiffs would need to show this, this</p>

<p style="text-align: right;">Page 290</p> <p>1 standard that you've set?</p> <p>2 A. There -- again, there is</p> <p>3 50 years of data showing numerous studies,</p> <p>4 including many that I've cited in my report,</p> <p>5 that therapeutic doses of acetaminophen do</p> <p>6 not cause liver injury. The liver has an</p> <p>7 enormous amount of CYP2E1, so if you have an</p> <p>8 organ with even less CYP2E1, you are</p> <p>9 certainly not going to get therapeutic injury</p> <p>10 with therapeutic doses in that organ.</p> <p>11 Q. Sorry. You are -- you are</p> <p>12 addressing that we need to show -- plaintiffs</p> <p>13 need to show that CYP2E1 enzyme is present in</p> <p>14 the brain at levels at least comparable to</p> <p>15 the liver in order to establish biological</p> <p>16 plausibility that acetaminophen causes</p> <p>17 developmental neurotoxicity through NAPQI</p> <p>18 expression, right?</p> <p>19 A. My statement is that in order</p> <p>20 for -- to establish the biological</p> <p>21 plausibility, right, that maternal ingestion</p> <p>22 of recommended doses of acetaminophen could</p> <p>23 cause neurodevelopmental toxicity, you would</p> <p>24 need to have, at a minimum, the amount of</p> <p>25 CYP2E1 in the brain that you find in the</p>	<p style="text-align: right;">Page 292</p> <p>1 don't cause toxicity. And again, when I used</p> <p>2 the term "minimal," this is relative to the</p> <p>3 other doses in the study. Again, you can</p> <p>4 look at Figure 2A and you can still see that</p> <p>5 there was loss of glutathione, even at that</p> <p>6 very low dose.</p> <p>7 Q. But here's the problem. You</p> <p>8 didn't study what concurrent treatment, what</p> <p>9 constant chronic therapy on acetaminophen</p> <p>10 over a period of time at recommended doses</p> <p>11 would do to address protein binding in a</p> <p>12 brain.</p> <p>13 You're a single-overdose liver</p> <p>14 scientist, and that's what you've presented</p> <p>15 in your report by and large.</p> <p>16 A. As I've --</p> <p>17 MR. COHEN: Objection, form.</p> <p>18 Go ahead.</p> <p>19 A. As I've discussed earlier in</p> <p>20 the day, the plaintiff experts also rely on</p> <p>21 studies of single acute overdoses, and what</p> <p>22 we know about -- when you take multiple doses</p> <p>23 of acetaminophen -- I stated this in my</p> <p>24 report -- is that the steady-state plasma</p> <p>25 concentration is around 50 micromole per</p>
<p style="text-align: right;">Page 291</p> <p>1 liver.</p> <p>2 Q. What literature do you cite</p> <p>3 to -- what can you point plaintiffs to and</p> <p>4 the court to to support that statement?</p> <p>5 That's all I'm asking.</p> <p>6 A. Okay. So again, there's</p> <p>7 50 years of literature. If you'd like me to</p> <p>8 give you one example, you can look at my 2013</p> <p>9 study where I'm the first author. That would</p> <p>10 be this study, which I believe you marked as</p> <p>11 Exhibit P803.</p> <p>12 Q. Uh-huh. Let's pause with that</p> <p>13 one, okay. We'll talk about that one.</p> <p>14 MR. COHEN: What's the number?</p> <p>15 MR. JANUSH: P803.</p> <p>16 BY MR. JANUSH:</p> <p>17 Q. Doesn't P803, your own</p> <p>18 literature, conclude that you were able to</p> <p>19 detect protein binding after treatment with</p> <p>20 15 milligrams per kilogram of APAP at earlier</p> <p>21 time points with only minimal loss of liver</p> <p>22 GSH, glutathione?</p> <p>23 A. As we discussed earlier, again,</p> <p>24 protein adducts are necessary but not</p> <p>25 sufficient for toxicity; protein adducts</p>	<p style="text-align: right;">Page 293</p> <p>1 milliliter, which is very low. That's a</p> <p>2 concentration that doesn't cause any kind of</p> <p>3 toxicity in the liver.</p> <p>4 And so some of the reports</p> <p>5 discussed by Dr. Louie where they might</p> <p>6 purport to provide data on longer exposures</p> <p>7 to acetaminophen, or where at least</p> <p>8 Dr. Louie, for example, interprets the data</p> <p>9 that way, they're looking at concentrations</p> <p>10 that are far higher than that.</p> <p>11 BY MR. JANUSH:</p> <p>12 Q. What's the amount of protein</p> <p>13 binding in the fetal brain that would be</p> <p>14 problematic?</p> <p>15 A. I can't say. I mean, I can</p> <p>16 tell you what we typically see in the liver,</p> <p>17 which, I mean, you can --</p> <p>18 Q. Would you agree liver injury is</p> <p>19 not equal to brain injury, right?</p> <p>20 A. That's quite a broad statement.</p> <p>21 Again, the hypotheses that I'm addressing</p> <p>22 about NAPQI, protein binding in the brain,</p> <p>23 they come from the plaintiffs' experts, and</p> <p>24 that's what I've been asked to address. And</p> <p>25 they -- the plaintiffs' experts derived them</p>

<p style="text-align: right;">Page 294</p> <p>1 from what happens in the liver.</p> <p>2 Q. But when seeking to cite to</p> <p>3 literature that supports your report, you</p> <p>4 cited me to your own literature from 2013,</p> <p>5 right?</p> <p>6 A. So again, what we see in the</p> <p>7 liver, and again, the plaintiffs' experts are</p> <p>8 giving their hypotheses that I'm simply</p> <p>9 addressing from data in the liver, so that's</p> <p>10 the context that we're working in, right?</p> <p>11 What we see in the liver is that you have</p> <p>12 extremely high CYP2E1 levels, and you still</p> <p>13 have no toxicity at therapeutic doses ever --</p> <p>14 or at least clinically significant liver</p> <p>15 injury. Let's put it that way.</p> <p>16 So if you have an organ with</p> <p>17 even less CYP2E1, then certainly therapeutic</p> <p>18 doses would not be expected to cause injury</p> <p>19 within the framework that has been</p> <p>20 established by the plaintiffs' experts to</p> <p>21 which I am responding.</p> <p>22 Q. Is it your opinion that because</p> <p>23 at least 10 grams in a single dose of</p> <p>24 acetaminophen is required for liver injury,</p> <p>25 that similar levels of glutathione depletion</p>	<p style="text-align: right;">Page 296</p> <p>1 necrotic cell death.</p> <p>2 You agree with that, right?</p> <p>3 MR. COHEN: I'm sorry, which</p> <p>4 page are you on?</p> <p>5 MR. JANUSH: Introduction.</p> <p>6 A. In the liver after overdose.</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. And you also address that</p> <p>9 protein binding APAP-CYS could be detected in</p> <p>10 serum from humans after only therapeutic</p> <p>11 doses, citing to Heard, right?</p> <p>12 A. Yeah. Again, protein binding</p> <p>13 is necessary but not sufficient for toxicity.</p> <p>14 Q. Well, if protein binding occurs</p> <p>15 over an extensive period of time, have you</p> <p>16 considered what the impact would be when</p> <p>17 someone is -- a maternal -- a pregnant woman</p> <p>18 is taking Tylenol or acetaminophen on a daily</p> <p>19 basis, multiple doses throughout the day?</p> <p>20 MR. COHEN: Objection, form.</p> <p>21 Go ahead.</p> <p>22 A. So what you're -- what you seem</p> <p>23 to be suggesting or that my interpretation is</p> <p>24 that formation of more adducts over time</p> <p>25 would cause greater injury, so actually, we</p>
<p style="text-align: right;">Page 295</p> <p>1 are necessary to trigger developmental</p> <p>2 neurotoxicity through NAPQI expression in the</p> <p>3 embryonic or fetal brain?</p> <p>4 A. Again, we're working off of</p> <p>5 what we know in the liver, which is the</p> <p>6 framework that the plaintiffs' experts have</p> <p>7 provided. Based on what we know happens in</p> <p>8 the liver, which the plaintiffs' experts</p> <p>9 reference, I would assume that you would have</p> <p>10 to have extensive GSH depletion, glutathione</p> <p>11 depletion.</p> <p>12 Q. In your literature at P803 that</p> <p>13 we have before us, haven't you published --</p> <p>14 haven't you included statements concluding</p> <p>15 that a greater than 70% reduction is not</p> <p>16 necessary -- and we're talking about</p> <p>17 glutathione reduction -- is not necessary for</p> <p>18 NAPQI-induced hepatotoxicity?</p> <p>19 A. No, I have not.</p> <p>20 Q. I might have the article wrong,</p> <p>21 but let me see.</p> <p>22 What this article does say,</p> <p>23 however, is that binding to proteins, and</p> <p>24 mitochondrial proteins, causes oxidative</p> <p>25 stress and mitochondrial damage resulting in</p>	<p style="text-align: right;">Page 297</p> <p>1 have done -- well, let me rephrase that.</p> <p>2 I'm aware of studies -- at</p> <p>3 least one study that has been done where I</p> <p>4 believe they did look at multiple dosing of</p> <p>5 acetaminophen, even at actually fairly high</p> <p>6 doses, but still sub-hepatotoxic, and they</p> <p>7 didn't find any evidence of toxicity.</p> <p>8 Regardless, even --</p> <p>9 BY MR. JANUSH:</p> <p>10 Q. Is that study cited in your</p> <p>11 report?</p> <p>12 A. I -- I don't recall for sure,</p> <p>13 but I don't believe I stated that one.</p> <p>14 Q. Why not?</p> <p>15 A. Well, your --</p> <p>16 Q. Given that this isn't a</p> <p>17 single-use overdose case, why not?</p> <p>18 A. So it's -- it's not a study of</p> <p>19 therapeutic dosing, and --</p> <p>20 Q. Nor are your single-use</p> <p>21 overdose cases, right? Those case reports</p> <p>22 and the published literature are not</p> <p>23 therapeutic dosing, are they?</p> <p>24 MR. COHEN: Objection,</p> <p>25 interrupted the witness.</p>

<p style="text-align: right;">Page 298</p> <p>1 Go ahead.</p> <p>2 A. So -- right. If you're</p> <p>3 concerned about single dosing and overdosing,</p> <p>4 again, the plaintiffs' experts rely on the</p> <p>5 same kinds of studies for their opinions.</p> <p>6 I mean, in addition to that,</p> <p>7 that's where most of the data on</p> <p>8 acetaminophen toxicity come from, so we kind</p> <p>9 of have to rely on it.</p> <p>10 But there are studies of</p> <p>11 long-term therapeutic dosing in humans, and</p> <p>12 they never show clinically significant liver</p> <p>13 injury that's clearly due to the</p> <p>14 acetaminophen.</p> <p>15 BY MR. JANUSH:</p> <p>16 Q. Dr. McGill, for a while today</p> <p>17 we've addressed the notion that you've</p> <p>18 published, including at footnote 803 --</p> <p>19 excuse me, Exhibit 803, that protein binding</p> <p>20 can occur without much loss of GSH, right?</p> <p>21 A. Again, this is a -- there is</p> <p>22 loss of GSH. Minimal or much loss of GSH in</p> <p>23 my paper that we've discussed was a relative</p> <p>24 term compared to the other doses, the</p> <p>25 overdoses. There's still loss of GSH.</p>	<p style="text-align: right;">Page 300</p> <p>1 sufficient GSH, is what I meant to say, that</p> <p>2 the brain has sufficient GSH to detoxify any</p> <p>3 NAPQI that would be expressed. That's what I</p> <p>4 meant to say.</p> <p>5 You take that position, right?</p> <p>6 MR. COHEN: Objection, form.</p> <p>7 A. We know from the studies that</p> <p>8 I've cited in my report on glutathione levels</p> <p>9 in humans that the brain, including the fetal</p> <p>10 brain, possesses millimole per liter</p> <p>11 concentration of glutathione.</p> <p>12 Considering you only have</p> <p>13 micromole per liter -- so on the order of a</p> <p>14 thousand-fold lower concentrations of</p> <p>15 acetaminophen in the plasma, and only a small</p> <p>16 portion of that ever gets converted to NAPQI,</p> <p>17 I think it's very safe to say that there's</p> <p>18 sufficient glutathione in the brain to</p> <p>19 detoxify -- including the fetal brain -- to</p> <p>20 detoxify any NAPQI that might be formed</p> <p>21 there.</p> <p>22 Again, there's absolutely no</p> <p>23 evidence for NAPQI formation in the brain</p> <p>24 even after massive overdoses of</p> <p>25 acetaminophen. Individuals, other groups</p>
<p style="text-align: right;">Page 299</p> <p>1 Q. And the protein binding we are</p> <p>2 addressing in this article is NAPQI</p> <p>3 expression, right?</p> <p>4 A. The protein adducts that form</p> <p>5 are a result of NAPQI reacting with proteins.</p> <p>6 Q. Dr. McGill, you also claim that</p> <p>7 there's an immediate detoxification of NAPQI</p> <p>8 in the brain due to the presence of</p> <p>9 glutathione, right?</p> <p>10 A. Can you point me to that</p> <p>11 statement that you're quoting?</p> <p>12 Q. I'm just saying you claim that,</p> <p>13 that the brain would detoxify any NAPQI</p> <p>14 present because the brain has sufficient</p> <p>15 NAPQI to detoxify -- sufficient --</p> <p>16 A. Yeah, I --</p> <p>17 MR. COHEN: Wait, wait.</p> <p>18 MR. JANUSH: Excuse me.</p> <p>19 THE WITNESS: Sorry, I should</p> <p>20 not have interrupted.</p> <p>21 MR. COHEN: Let him --</p> <p>22 Will you start the question</p> <p>23 again? It got interrupted.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. I mean -- that the brain has</p>	<p style="text-align: right;">Page 301</p> <p>1 have looked at that, acetaminophen-protein</p> <p>2 binding, as a surrogate for NAPQI formation.</p> <p>3 They do not find any evidence for it.</p> <p>4 And -- well, I'll just leave it</p> <p>5 at that.</p> <p>6 BY MR. JANUSH:</p> <p>7 Q. At paragraph 41, you wrote:</p> <p>8 According to this database -- and the</p> <p>9 database that you are addressing is the Human</p> <p>10 Protein Atlas database -- the adult human</p> <p>11 brain has less than one-seven-hundredth of</p> <p>12 the CYP2E1 mRNA than in the adult liver, even</p> <p>13 using the highest value in the brain measured</p> <p>14 in the cerebellum. Even if small amounts of</p> <p>15 mRNA are detected, the corresponding protein</p> <p>16 might not be made from the mRNA (i.e.,</p> <p>17 expressed).</p> <p>18 And you also address that</p> <p>19 there's no indication in their data with</p> <p>20 respect to the database that CYP2E1 is more</p> <p>21 highly expressed in the brain during</p> <p>22 development compared to adulthood, right?</p> <p>23 A. Yes.</p> <p>24 Q. Just because something appears</p> <p>25 in a smaller amount doesn't mean that it</p>

<p style="text-align: right;">Page 302</p> <p>1 fails to present clinical manifestations, 2 right?</p> <p>3 A. In the case of a -- in this 4 case it does because, again, you don't 5 have -- right, okay. We're working with the 6 liver here because that's where we have most 7 of our data, okay, on acetaminophen toxicity. 8 It's also the framework established by the 9 plaintiffs' experts.</p> <p>10 We know in the liver, at 11 therapeutic doses, you do not get clinically 12 significant liver injury. The liver has an 13 enormous amount of P450. If you find that 14 there's another organ that has less P450, 15 specifically less CYP2E1, then you certainly 16 would not expect therapeutic doses to cause 17 any injury there.</p> <p>18 Q. I'm going to present to you the 19 Bhamre article as P818.</p> <p>20 (Whereupon, Deposition 21 Exhibit P818, Purification of Multiple 22 Forms of Cytochrome P450 from a Human 23 Brain and Reconstitution of Catalytic 24 Activities, by Bhamre et al., was 25 marked for identification.)</p>	<p style="text-align: right;">Page 304</p> <p>1 Q. Can you point anywhere in this 2 article where there's a reflection that there 3 was acetaminophen use?</p> <p>4 A. This is not a study of 5 acetaminophen, nor did I cite it as such, 6 right? I cited this as evidence that there's 7 no CYP2E1 in the brain --</p> <p>8 Q. I get that.</p> <p>9 A. -- in the human brain.</p> <p>10 Q. I understand that.</p> <p>11 But isn't acetaminophen -- 12 doesn't acetaminophen induce CYP2E1? Isn't 13 CYP2E1 highly inducible due to acetaminophen?</p> <p>14 A. No.</p> <p>15 Q. You disagree that -- you don't 16 believe CYP2E1 is inducible?</p> <p>17 A. I do not. No, no, let me 18 rephrase that. CYP2E1 is not inducible by -- 19 well, there is no clear reproducible, 20 rigorous evidence that acetaminophen induces 21 CYP2E1.</p> <p>22 Q. Interesting.</p> <p>23 A. In fact, there's conflicting 24 data, for example, Bao 2020, which actually 25 shows, when you look at messenger RNA protein</p>
<p style="text-align: right;">Page 303</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. Now, you address Bhamre and 3 claim that: Bhamre reported virtually no 4 CYP2E1 immunoreactivity on immunoblots of 5 cytochrome P450 fractions purified from a 6 male human brain; is that right?</p> <p>7 A. Yes.</p> <p>8 Q. Okay. So in the study, the 9 brain that was being analyzed was 11 hours 10 postmortem, right?</p> <p>11 A. Sorry. Just to clarify your 12 prior question, you did say CYP2E1 13 immunoreactivity, correct, specifically?</p> <p>14 Q. I said CYP2E1 immunoreactivity.</p> <p>15 A. Just to be sure that's what 16 we're talking about.</p> <p>17 Q. Immunoblots of cytochrome P450 18 fractions purified from a male human brain.</p> <p>19 A. Yes, CYP2E1 immunoreactivity in 20 those fractions.</p> <p>21 Q. Yeah. So this was a decedent 22 from a motor vehicle accident having donated 23 their brain, apparently, and the brain is 24 being studied 11 hours postmortem, right?</p> <p>25 A. That's what they state here.</p>	<p style="text-align: right;">Page 305</p> <p>1 level and CYP2E1 activity in the brain of 2 mice at different ages, what they find 3 consistently is a decrease, in fact, in 4 CYP2E1 levels in the liver.</p> <p>5 Q. So I'm going to turn back to 6 that later. We're going to talk about 7 inducibility, but I'm going to stay on this 8 document.</p> <p>9 So number one, you agree that 10 the brain is being studied 11 hours 11 postmortem, right?</p> <p>12 A. That's what they state here.</p> <p>13 Q. Okay. And I'm going to bet 14 you're going to agree with this too: CYP2E1 15 has a half-life of only about four hours in 16 the absence of a stabilizing substrate or 17 ligand as is the case after death, right?</p> <p>18 A. I have no idea what you're 19 getting -- where you're getting that from, so 20 I -- I can't say.</p> <p>21 MR. WATTS: Can we take a 22 break?</p> <p>23 MR. JANUSH: Sure.</p> <p>24 THE VIDEOGRAPHER: We're going 25 off the record. The time is 3:49.</p>

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1 (Recess taken, 3:49 p.m. to
2 3:57 p.m. CDT)
3 THE VIDEOGRAPHER: We're going
4 back on record. The time is 3:57.
5 BY MR. JANUSH:
6 Q. Passing you Plaintiffs'
7 Exhibit 819.
8 (Whereupon, Deposition
9 Exhibit P819, CYP2E1 and Oxidative
10 Liver Injury by Alcohol, by Lu et al.,
11 was marked for identification.)
12 A. Thank you.
13 BY MR. JANUSH:
14 Q. So I left a little sticky on it
15 to make it easier for you to turn to the
16 page -- you'd stated before the break that
17 you had no idea where I was getting that
18 half-life from.
19 I'm presenting you with a
20 National Institutes of Health manuscript
21 addressing -- titled CYP2E1 and Oxidative
22 Liver Injury by Alcohol, and the author is
23 Yongke Lu and Arthur Cederbaum.
24 If you turn to page 9, where I
25 put a sticker to make it easier for you --

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1 A. Uh-huh.
2 Q. -- you'll see a discussion
3 concerning the half-life of CYP2E1. And so
4 the author notes that -- towards the bottom
5 of the first -- of the big paragraph: This
6 system was used to evaluate turnover of the
7 rabbit CYP2E1, which was rapid with a
8 half-life of 3.9 h, hours, in the absence of
9 a stabilizing substrate or ligand. Addition
10 of the latter decreased the degradation of
11 CYP2E1. We observed similar results in HepG2
12 cells expressing CYP2E1 as the half-life of
13 human CYP2E1 was about 3 to 6 hours in the
14 absence of a substrate or ligand, and was
15 elevated in the presence of various
16 substrates and ligands.
17 Do you see that?
18 A. Yeah, I see this --
19 Q. So that's where I was getting
20 it from with respect to the published
21 findings concerning the half-life of CYP2E1.
22 Had you ever, before today,
23 studied about or learned about the CYP2E1
24 half-life in the absence of a stabilizing
25 substrate or ligand?

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1 A. No, not specifically.
2 Q. It's kind of relevant when
3 studying deceased brains, right?
4 A. I would note here this is -- it
5 appears -- I haven't had an opportunity to
6 read the whole paper, and actually, this
7 appears to be a review.
8 It appears to me they're
9 talking about a situation in cells. Cells
10 have many ways -- healthy cells, right, live
11 cells, they -- well, okay. So they mention
12 that --
13 Q. Let me help you. I don't want
14 to -- I'm not trying to --
15 MR. COHEN: Whoa. Whoa. Let
16 him finish.
17 THE WITNESS: Excuse me.
18 MR. COHEN: Let him finish.
19 A. They say "this system." Above
20 that, they appear to be talking about HepG2
21 cells. So yeah, right here: Huan and Koop
22 established a tetracycline-controlled rabbit
23 CYP2E1-expressing system in HeLa cells in
24 culture. This system was used to evaluate
25 turnover of the rabbit CYP2E1, which was

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1 rapid with a half-life of 3.9 hours.
2 This is done in live, viable
3 functional cells. Proteins constantly turn
4 over in live cells. This is part of just
5 protein maintenance of -- normal protein
6 levels, maintaining protein homeostasis.
7 It's part of protein quality control.
8 Dead cells that aren't
9 functional, I have no idea if they turn over
10 proteins or at what rates or what half-life,
11 any protein, certainly not CYP2E1. This --
12 therefore, in my opinion, this has no
13 relevance to this Bhamre study.
14 BY MR. JANUSH:
15 Q. Wouldn't a dead brain have a
16 lesser half-life than a living brain when it
17 comes to CYP2E1 expression and -- and
18 calculation?
19 A. No, not necessarily. Because
20 again, functional cells maintain homeostasis,
21 right? That means part of that is
22 maintaining a certain level of proteins. You
23 don't want to just make a ton of some protein
24 and let it get out of control. You have to
25 tightly control your functions. You're

<p style="text-align: right;">Page 310</p> <p>1 maintaining homeostasis on a live cell.</p> <p>2 I don't think dead cells</p> <p>3 maintain homeostasis. I don't think dead</p> <p>4 cells do quality control. I have no idea</p> <p>5 what the protein turnover rate is for any</p> <p>6 protein in a dead cell, much less CYP2E1.</p> <p>7 This paper does not touch on that.</p> <p>8 Q. But a dead cell would be more</p> <p>9 prone for CYP2E1's half-life to be shortened,</p> <p>10 not lengthened, right?</p> <p>11 A. Once again, you absolutely</p> <p>12 cannot say that. Again, live functional</p> <p>13 viable cells maintain protein homeostasis.</p> <p>14 They maintain presently quality control. I</p> <p>15 would imagine dead cells don't do that.</p> <p>16 Q. So when you say "I would</p> <p>17 imagine," are you just speculating?</p> <p>18 MR. COHEN: Objection, form.</p> <p>19 A. Speculating? No more than you</p> <p>20 are.</p> <p>21 BY MR. JANUSH:</p> <p>22 Q. Right. But I'm an attorney and</p> <p>23 you're the expert here, right?</p> <p>24 MR. COHEN: Objection, form.</p> <p>25 ///</p>	<p style="text-align: right;">Page 312</p> <p>1 accident. You agree with that, right?</p> <p>2 A. The authors state that it's a</p> <p>3 human brain from a male subject, aged</p> <p>4 50 years, obtained at autopsy. Death was due</p> <p>5 to an instant -- was instant due to a traffic</p> <p>6 accident, excuse me, and the brain was</p> <p>7 obtained 11 hours postmortem.</p> <p>8 Q. And the subject had no known</p> <p>9 neurological disorders, right?</p> <p>10 A. That's a sentence in the</p> <p>11 Methods section.</p> <p>12 Q. Yep. And nothing in this</p> <p>13 entire article is addressing acetaminophen,</p> <p>14 right?</p> <p>15 A. Yeah. Again, I didn't cite it</p> <p>16 for any statement about acetaminophen. I</p> <p>17 cited it for a statement about CYP2E1 levels</p> <p>18 in the brain. So whether or not</p> <p>19 acetaminophen is in it is irrelevant.</p> <p>20 Q. It's actually not irrelevant if</p> <p>21 CYP2E1 is something that induces -- excuse</p> <p>22 me.</p> <p>23 If acetaminophen induces</p> <p>24 CYP2E1, that's not irrelevant, is it?</p> <p>25 A. Well, again, there's no</p>
<p style="text-align: right;">Page 311</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. You're the scientist, I'm not,</p> <p>3 right?</p> <p>4 A. You have not presented any data</p> <p>5 to me that shows that this half-life is</p> <p>6 relevant in a human body postmortem.</p> <p>7 Q. I showed you a living human and</p> <p>8 what the half-life is --</p> <p>9 A. Sorry. You didn't show a</p> <p>10 living human. You showed a living cell</p> <p>11 system.</p> <p>12 Q. A living cell system. Fair</p> <p>13 enough.</p> <p>14 A. That's an important distinction</p> <p>15 also, because this is cell culture. Cell</p> <p>16 cultures, especially HeLa cells, very</p> <p>17 famously, are aberrant. Normal cells don't</p> <p>18 grow on plastic like that, right? And HeLa</p> <p>19 cells are very famously not normal. There's</p> <p>20 a whole book written about this, a very</p> <p>21 popular scientific nonfiction book.</p> <p>22 Q. And so you agree, though, that</p> <p>23 this was a study of a single human brain of a</p> <p>24 male subject, aged 50, obtained at autopsy</p> <p>25 following an instant death due to a traffic</p>	<p style="text-align: right;">Page 313</p> <p>1 consistent reproducible, rigorous scientific</p> <p>2 evidence that acetaminophen induces CYP2E1.</p> <p>3 It's not a widely accepted idea in my field.</p> <p>4 In fact, there are conflicting data for it.</p> <p>5 Q. The next article you address is</p> <p>6 Boutelet-Bochan from 1997. And with regard</p> <p>7 to Boutelet-Bochan, you take the position</p> <p>8 that the study did not measure CYP2E1 protein</p> <p>9 in the brain, right?</p> <p>10 A. Correct, that's a statement</p> <p>11 that I've made.</p> <p>12 Q. You agree that the study</p> <p>13 authors used standard reverse</p> <p>14 transcription-polymerase chain reaction and</p> <p>15 detected CYP2E1 mRNA in brain, right?</p> <p>16 A. They used three different</p> <p>17 methods to look at messenger RNA.</p> <p>18 Q. Yeah, I'm just addressing that</p> <p>19 one of the three.</p> <p>20 And you agree that mRNA is the</p> <p>21 precursor to the protein CYP2E1, right?</p> <p>22 A. The central dogma of biology is</p> <p>23 you have DNA that gets transcribed to RNA,</p> <p>24 which is then translated to protein.</p> <p>25 Q. Did the authors actually detect</p>

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1 CYP2E1 mRNA in nine of the ten brains that
 2 were studied?

3 A. Can you produce the article,
 4 please, just to refresh my memory.

5 Q. Sure can. Exhibit P820.
 6 (Whereupon, Deposition
 7 Exhibit P820, Expression of CYP2E1
 8 during Embryogenesis and Fetogenesis
 9 in Human Cephalic Tissues:
 10 Implications for the Fetal Alcohol
 11 Syndrome, by Boutelet-Bochan et al.,
 12 was marked for identification.)

13 BY MR. JANUSH:

14 Q. And I'm going to turn your
 15 attention to page 445 at the Discussion,
 16 where at the bottom of the paragraph, above
 17 Figure 3, the authors write: With RT-PCR,
 18 the assay of highest sensitivity, strong
 19 signals were readily detectable in nine of
 20 ten human prenatal cephalic samples.

21 Do you see that?

22 A. I see that statement.

23 Q. Lack of detection in one sample
 24 remains unexplained, but may be due to
 25 genetic or environmental factors.

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1 And then it goes into the next
 2 page, and there's a Table 1. Do you see the
 3 Table 1 on the next page?

4 A. I do.

5 Q. And when we look at the RT-PCR,
 6 the brains there, the 10, we see nine of ten
 7 all with plus, plus, plus for brain tissue,
 8 intensity of observed signals.

9 Do you see that?

10 A. I see it. I also see below
 11 where they did northern blotting.

12 Q. I'm addressing RT-PCR, just say
 13 with me.

14 A. I also see below where they did
 15 northern blot --

16 Q. I know you want to testify
 17 about questions I haven't asked you, but I'm
 18 only addressing RT-PCR. Do you see that --

19 A. I would like to finish my
 20 answer.

21 Q. No, no, no. Your lawyer will
 22 get the chance to question you, and you can
 23 answer anything he asks you. But I'm only
 24 asking about RT-PCR.

25 So three pluses. And do you

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1 see at the bottom underneath the table, plus,
 2 plus, plus says strong?

3 Do you see that?

4 A. I see it.

5 Q. Okay. You left that out of
 6 your report in the sense that you left out
 7 that nine of ten brains demonstrated strong
 8 signals of mRNA CYP2E1, didn't you, under the
 9 RT-PCR analysis?

10 A. No, I address these data in my
 11 report by pointing out that there's a serious
 12 methodological flaw with the way they did the
 13 RT-PCR experiment.

14 Q. I appreciate that you addressed
 15 the flaw, and we're going to get there in a
 16 minute.

17 You left out that the authors
 18 found a strong signal of the precursor mRNA
 19 to CYP2E1 in prenatal human brains, in nine
 20 of ten prenatal human brains. You left that
 21 out of your report, right?

22 A. So as we discussed at length,
 23 the framework set up by the plaintiffs'
 24 experts is looking at what happens in the
 25 brain in relation to what we know about the

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1 liver, right.

2 You cannot do a -- you
 3 cannot -- you know, it's fine if you just
 4 want to use a -- by the way, extremely
 5 sensitive method -- to say, okay, there might
 6 be some CYP2E1 in the brain. I haven't
 7 disputed that in my report. I've said that
 8 there are negligible levels or little to no.

9 And when I say no, that's
 10 supported by data showing that in some
 11 studies when it's undetectable completely.

12 So everything has to be viewed
 13 here in reference to a comparison with the
 14 liver. The way that they did this RT-PCR
 15 part in Table 1 is severely methodologically
 16 flawed and can't be relied on for that
 17 comparison.

18 MR. JANUSH: Move to strike,
 19 nonresponsive.

20 BY MR. JANUSH:

21 Q. I only asked you if you left
 22 out of your report that nine of ten brains
 23 showed strong mRNA CYP2E1 expression.

24 A. Again --

25 Q. Did you leave that out of your

<p style="text-align: right;">Page 318</p> <p>1 report?</p> <p>2 A. Again, the framework that we're</p> <p>3 working within, which was established in the</p> <p>4 plaintiffs' experts' reports, is that you</p> <p>5 have to consider the evidence -- consider</p> <p>6 data in the brain in the context of what we</p> <p>7 know about the liver. We discussed that at</p> <p>8 length. It's a very relevant piece of</p> <p>9 information here.</p> <p>10 The relevant data is when you</p> <p>11 compare with the liver. And by the way, this</p> <p>12 is -- well, we can come back to that later.</p> <p>13 So the relevant data here is</p> <p>14 that you compare to the liver, and that</p> <p>15 comparison is impossible with the RT-PCR</p> <p>16 method that they've used here. This is --</p> <p>17 this is a method that's a binary result</p> <p>18 essentially -- it's essentially yes or no, is</p> <p>19 there some messenger RNA there. With that</p> <p>20 specific method, the answer was yes. With</p> <p>21 the other methods that they applied, the</p> <p>22 answer is either completely no across the</p> <p>23 board or conflicting --</p> <p>24 Q. So --</p> <p>25 A. -- equivocal.</p>	<p style="text-align: right;">Page 320</p> <p>1 A. It's a meaningless result the</p> <p>2 way the experiment was done.</p> <p>3 Q. Yes or no? I appreciate that</p> <p>4 you don't want to give me an answer, but it's</p> <p>5 a yes, right?</p> <p>6 A. No, I'm giving you the</p> <p>7 scientific answer, the correct answer. You</p> <p>8 understand? The way that they have done this</p> <p>9 method, they cannot say, oh, there's a ton of</p> <p>10 people with CYP2E1 here.</p> <p>11 They can say, oh, we've got a</p> <p>12 pretty strong signal in the PCR, but the PCR,</p> <p>13 again, the way that they've done it, they</p> <p>14 cannot compare with the liver, and that is</p> <p>15 our standard.</p> <p>16 As we've discussed, as the</p> <p>17 expert -- plaintiffs' experts established in</p> <p>18 their framework for -- that I'm responding</p> <p>19 to.</p> <p>20 Q. Dr. McGill --</p> <p>21 A. The data are severely flawed.</p> <p>22 Q. Dr. McGill, you criticize the</p> <p>23 manner in which the polymerase chain reaction</p> <p>24 was run because you say it should have been</p> <p>25 stopped during the exponential phase of</p>
<p style="text-align: right;">Page 319</p> <p>1 Q. So I don't see yes or no on the</p> <p>2 table. I see plus, plus, plus, plus for very</p> <p>3 strong signal, plus, plus, plus for strong,</p> <p>4 plus, plus for good, plus for detectable -- I</p> <p>5 guess that would be a yes or no -- and plus</p> <p>6 or minus for questionably detectable. And</p> <p>7 minus -- actually, that's the no. Minus for</p> <p>8 not detectable. And ND, not determined.</p> <p>9 Do you see that underneath the</p> <p>10 table?</p> <p>11 A. Oh, I see the definitions.</p> <p>12 Q. Okay.</p> <p>13 A. I --</p> <p>14 Q. I just asked if you saw it.</p> <p>15 You answered me.</p> <p>16 Now, on this, three pluses is</p> <p>17 the second-to-highest relative intensity of</p> <p>18 observed signals in nine of ten fetal brains</p> <p>19 for mRNA CYP2E1 expression, isn't it? Yes or</p> <p>20 no?</p> <p>21 MR. COHEN: Object. Object to</p> <p>22 the form.</p> <p>23 Go ahead.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. Yes or no?</p>	<p style="text-align: right;">Page 321</p> <p>1 amplification before the signal plateaus.</p> <p>2 But in this case, the authors</p> <p>3 ran all polymerase chain reactions for 30</p> <p>4 cycles, right?</p> <p>5 A. Yes, which is what you should</p> <p>6 not do.</p> <p>7 Q. And isn't it the case that by</p> <p>8 30 cycles, when you run a polymerase chain</p> <p>9 reaction by 30 cycles, it's generally</p> <p>10 accepted that any identifiable signal will</p> <p>11 have reached a plateau?</p> <p>12 A. That's exactly the issue.</p> <p>13 They -- the issue is not that -- the question</p> <p>14 is when they reach the plateau, right?</p> <p>15 So when you do that, you can't</p> <p>16 make comparisons if you're stopping</p> <p>17 everything after they plateau. You've</p> <p>18 exceeded the dynamic range of the assay. You</p> <p>19 can no longer get a higher result for one</p> <p>20 sample that actually has a higher level.</p> <p>21 They would all have the same level.</p> <p>22 So by stopping at 30 cycles,</p> <p>23 they have effectively ruined the experiment,</p> <p>24 unless their only goal is to say yes or no,</p> <p>25 there's messenger RNA for CYP2E1 there. So</p>

<p style="text-align: right;">Page 322</p> <p>1 that's all you can get from that set of data.</p> <p>2 Yes, they found some messenger</p> <p>3 RNA. How much was there? It's impossible to</p> <p>4 say.</p> <p>5 Q. According to them, three plus,</p> <p>6 plus strength, right?</p> <p>7 A. I don't believe anywhere in</p> <p>8 their methods section they described that</p> <p>9 grading system.</p> <p>10 Q. Well --</p> <p>11 A. So I can't assess what that</p> <p>12 means. This is meaningless data.</p> <p>13 Q. Okay. So --</p> <p>14 A. Other than, okay, they found</p> <p>15 some CYP2E1 messenger RNA.</p> <p>16 Q. So -- but by comparison, given</p> <p>17 that you didn't provide your grading system</p> <p>18 on how you scored literature in this case,</p> <p>19 should we just discard your whole report as</p> <p>20 an irrelevancy?</p> <p>21 MR. COHEN: Objection, form.</p> <p>22 A. This is an entirely different</p> <p>23 question.</p> <p>24 BY MR. JANUSH:</p> <p>25 Q. Because it applies to you, it's</p>	<p style="text-align: right;">Page 324</p> <p>1 et al., was marked for</p> <p>2 identification.)</p> <p>3 BY MR. JANUSH:</p> <p>4 Q. And in Brzezinski, up at the</p> <p>5 Abstract portion, on the right-hand side, the</p> <p>6 last six lines, the authors write: There was</p> <p>7 a dramatic increase in human brain CYP2E1</p> <p>8 content around gestational day 50 and a</p> <p>9 fairly constant level was maintained</p> <p>10 throughout the early fetal period, until at</p> <p>11 least day 13 -- 113. The relatively low</p> <p>12 levels of the P450 isoform present in</p> <p>13 conceptual brain may be sufficient to</p> <p>14 generate reactive intermediates that elicit</p> <p>15 neuro embryotoxicity.</p> <p>16 Do you see that?</p> <p>17 A. I see their statement.</p> <p>18 Q. Do you agree that Brzezinski</p> <p>19 et al., in 1999 established that unconjugated</p> <p>20 APAP can reach fetal tissues, including the</p> <p>21 brain, and is locally biotransformed into the</p> <p>22 toxic reactive NAPQI by CYP2E1 expressed in</p> <p>23 the fetal brain?</p> <p>24 MR. COHEN: Objection, form.</p> <p>25 A. You're -- sorry, you're asking</p>
<p style="text-align: right;">Page 323</p> <p>1 different, right?</p> <p>2 A. No, absolutely not.</p> <p>3 MR. COHEN: No. Objection,</p> <p>4 form.</p> <p>5 A. This is actual -- well, we'll</p> <p>6 just leave it at that. It's a different</p> <p>7 question.</p> <p>8 BY MR. JANUSH:</p> <p>9 Q. Dr. McGill, are you aware that</p> <p>10 Boutelet-Bochan is part of the same research</p> <p>11 group as Brzezinski, who published on CYP2E1</p> <p>12 protein findings in 1999?</p> <p>13 A. I may have seen the</p> <p>14 affiliations. I don't know these</p> <p>15 individuals. I don't know who they work with</p> <p>16 or what groups they're a part of.</p> <p>17 Q. Okay. And I'd like to go to</p> <p>18 Brzezinski 1999 and --</p> <p>19 A. Do you have --</p> <p>20 Q. I will. I'm going pass it</p> <p>21 over. It's P821.</p> <p>22 (Whereupon, Deposition</p> <p>23 Exhibit P821, Catalytic Activity and</p> <p>24 Quantitation of Cytochrome P-450 2E1</p> <p>25 in Prenatal Human Brain, by Brzezinski</p>	<p style="text-align: right;">Page 325</p> <p>1 me if this study established that?</p> <p>2 BY MR. JANUSH:</p> <p>3 Q. Yes.</p> <p>4 A. Absolutely not.</p> <p>5 Q. It's your opinion that there's</p> <p>6 no evidence of NAPQI in fetal brain</p> <p>7 sufficient to cause injury; is that right?</p> <p>8 A. There's no evidence of NAPQI in</p> <p>9 the brain, period. We have no data about it</p> <p>10 in the fetal brain. So we assume, since, as</p> <p>11 you can see, for example, in the Allen</p> <p>12 Institute for Brain Sciences LMD microarray</p> <p>13 database, there's no substantial change --</p> <p>14 there's no substantial difference in</p> <p>15 expression in the fetus and adults in the</p> <p>16 brain of CYP2E1.</p> <p>17 So yeah, there's no reason to</p> <p>18 believe that fetal CYP2E1 is higher in the</p> <p>19 brain than in the adult. And we know you</p> <p>20 don't get adducts, at least in adult animals,</p> <p>21 in the brain, period. You don't get NAPQI.</p> <p>22 Q. I'm going to move to a</p> <p>23 different section here. I'm going to address</p> <p>24 at section -- subsection (b), Studies of</p> <p>25 Other CYP450s in Brain.</p>

<p style="text-align: right;">Page 326</p> <p>1 Here I'm going to address the 2 Warner study, cited at footnote 104, 3 addressed at paragraph 47. Published 4 studies -- let's see. 5 Warner et al., 1988, purified 6 total CYP450 content from rat brain and liver 7 and found that the yield of P450 from the 8 whole brain was 90 plus or minus 90 pmols 9 over g -- over grams of tissue, which is 10 approximately 1% of the level in liver 11 microsomes. 12 Do you see that? 13 A. I do. 14 Q. I'll hand you both that, marked 15 as 822. 16 (Whereupon, Deposition 17 Exhibit P822, Regional Distribution of 18 Cytochrome P450 in the Rat Brain: 19 Spectral Quantitation and Contribution 20 of P450b,e and P450c,d, by Warner 21 et al., was marked for 22 identification.) 23 BY MR. JANUSH: 24 Q. You also address that they, the 25 authors, also measured CYP450 content in</p>	<p style="text-align: right;">Page 328</p> <p>1 the brain, and they show that it's, you know, 2 in the range of 1 to 5% of what's in the 3 liver. That's total P450 content, not 4 CYP2E1. That's an important distinction. 5 It's also important to realize 6 not all P450s are involved in drug 7 metabolism. There are many other -- P450 is 8 a superfamily of enzymes. It's quite large. 9 There are many members, and they have many 10 different functions, cholesterol synthesis, 11 bioplastic synthesis, steroid synthesis. 12 So we don't know from the data 13 in this paper which isoforms -- well, exactly 14 what enzymes are contributing, what 15 percentage of these P450s are actually 16 relevant to drug metabolism. 17 In addition to that, there 18 actually are some data -- the last paragraph 19 of the Results section, that are -- I'm 20 sorry, I'll slow down a little bit -- that 21 are somewhat relevant to CYP2E1. So in that 22 section, they state -- I'll go ahead and read 23 it -- again, it's the last paragraph of the 24 Results section. 25 Ethoxycoumarin O-deethylase</p>
<p style="text-align: right;">Page 327</p> <p>1 various brain regions and found that it never 2 exceeded, you know, approximately 5% of the 3 liver content. 4 A. Uh-huh. 5 Q. Do you see that as well? 6 A. I do. 7 Q. After making this statement, 8 how can you go from the numbers addressed 9 from Warner with the brain levels being 10 approximately 1 to 5% of that of the liver to 11 what you say in paragraph 48, where you 12 address that CYP2E1 mRNA is approximately 13 1,000-fold lower in the brain than in the 14 liver? 15 A. Yeah, easily. 16 Q. How do you get there? 17 A. Very easily. 18 So for starters, my statement 19 about 1,000-fold lower in the brain than in 20 the liver is about CYP2E1. This study is not 21 about CYP2E1. Actually -- well, I'll come 22 back to that in just a minute. There is some 23 data relevant to CYP2E1. 24 What they've done in this paper 25 is they've isolated total P450 content from</p>	<p style="text-align: right;">Page 329</p> <p>1 activity -- which is a catalytic activity 2 characteristic of both P450b and P450c -- was 3 measurable in homogenates of thalamus and 4 cerebellum. Catalytic activity, expressed as 5 picomole of 7-hydroxycoumarin formed per hour 6 per gram of tissue was 392 in the thalamus 7 and 336 in the cerebellum. 8 I'll skip to the last sentence. 9 The corresponding value in 10 homogenates of livers of control rats is 11 1,200 nanomole per gram of tissue per hour. 12 Ethoxycoumarin deethylation has 13 been used in many studies as a marker of 14 CYP2E1 activity. It can be catalyzed by 15 other isoforms as well, but CYP2E1 16 contributes to that metabolism. 17 These 392 and 336 picogram -- 18 picomole -- excuse me -- per hour per gram 19 compared to the 1,200 nanomole per hour per 20 gram, that means there's -- they detected 21 about 0.03% of the activity in the liver in 22 the brain. 23 So in other words, there's 24 around or -- around 3,000-fold less in the 25 brain than the liver. This is the only piece</p>

<p style="text-align: right;">Page 330</p> <p>1 of data in this study that's relevant to 2 CYP2E1, and -- as far as I'm aware, as far as 3 I can recall, and that's -- actually makes my 4 statement pretty conservative because I said 5 1,000-fold lower. 6 In addition, the 1,000-fold 7 lower number, in the 16 studies that I cite 8 specifically on CYP2E1, right, 12 of which I 9 described in detail -- in contrast, by the 10 way, to what Dr. Louie stated in his rebuttal 11 report; he made the false claim that none of 12 the studies I cited addressed CYP2E1 13 specifically. 14 Of the 16 studies, from those 15 16 studies, I've provided 12 numbers where 16 they compared the brain levels to the liver, 17 and if you average those 12 numbers, it's 18 actually more than 1,000-fold lower in the 19 brain than in the liver. 20 So again, my statement is 21 actually conservative. 22 Q. And every one of the studies 23 that you address fails to address 24 acetaminophen, right? 25 A. I'm not citing those studies to</p>	<p style="text-align: right;">Page 332</p> <p>1 A. There are no reproduce -- there 2 are lots of conflicting data there. It's not 3 widely accepted in my field because -- I'm 4 sorry. 5 If your question -- if your 6 question is does acetaminophen induce CYP2E1, 7 that idea is not widely accepted in my field 8 because there are no consistent rigorous, 9 reproducible data showing that. 10 BY MR. JANUSH: 11 Q. Does ethanol induce CYP2E1? 12 A. I believe there's studies 13 showing that ethanol induces CYP2E1. 14 Q. Do you believe it's 15 biologically plausible for acetaminophen to 16 induce CYP2E1? 17 A. I mean, again, I've seen no 18 consistent reproducible data on that. I've 19 not seen a clear mechanism by which it would 20 happen, you know. 21 Q. Do you remember reviewing 22 Dr. Pearson's report which had the 23 single-cell Brain Bank image showing CYP2E1 24 expression in fetal brain? 25 A. Could you produce Dr. Pearson's</p>
<p style="text-align: right;">Page 331</p> <p>1 make any statement specifically about 2 acetaminophen. I'm citing those studies to 3 make a statement about the relative 4 expression of P4 -- CYP2E1 in the brain and 5 the liver. 6 Q. Right, in the absence of any -- 7 in the absence of any potentially inducible 8 acetaminophen, correct? None of the studies 9 you address have anything to do with 10 acetaminophen? 11 A. Sorry. So again, with regard 12 to the second part, I'm not citing them to -- 13 Q. I know, I've heard it a hundred 14 times. I get it. You're not citing them for 15 the premise of saying that it has anything to 16 do with acetaminophen. 17 A. I'd like to finish my response. 18 I'm citing them to support my 19 statements in that section about the relative 20 expression of CYP2E1 in the brain and the 21 liver. 22 Q. And to be clear, you take the 23 position that CYP2E1 is not inducible by 24 acetaminophen, right? 25 MR. COHEN: Objection, form.</p>	<p style="text-align: right;">Page 333</p> <p>1 report so I can refresh my memory? 2 Q. I probably can pull it up after 3 a break and put it on the screen. I didn't 4 anticipate, you know, using it to address 5 your report. 6 You have -- you read it. You 7 reviewed it. I'm asking if you remember the 8 single-cell Brain Bank image that showed 9 CYP2E1 activity? 10 A. My concern is that you may be 11 using a name for it that I would not use, and 12 so it's not -- I want to make sure it's clear 13 that we're talking about the same figure. 14 Q. Be happy to pull it up after 15 the break. Oh, perfect. 16 (Whereupon, Deposition 17 Exhibit P856, Excerpt from Pearson 18 Expert Report, was marked for 19 identification.) 20 BY MR. JANUSH: 21 Q. It's actually hard to see. 22 It's one -- one -- one page from Pearson's 23 report. It was on page 18. I'm sure I can 24 get it to the court technician electronically 25 and pull it up and blow it up for you.</p>

<p style="text-align: right;">Page 334</p> <p>1 I don't remember if you -- I</p> <p>2 don't know if you remember seeing that.</p> <p>3 A. I recall seeing it.</p> <p>4 Q. And? Do you have anything to</p> <p>5 comment on regarding it?</p> <p>6 A. If you have a specific</p> <p>7 question, I'll be happy to comment.</p> <p>8 Q. Are you disputing that CYP2E1</p> <p>9 levels have been observed by the Brain Bank,</p> <p>10 I believe it is, in fetal brain?</p> <p>11 A. Well, to be clear, this is</p> <p>12 messenger RNA data. It's not protein. So to</p> <p>13 say that CYP2E1 levels have been observed is</p> <p>14 not quite accurate based on these data alone.</p> <p>15 So what this figure shows is a</p> <p>16 comparison, as I recall, a comparison of</p> <p>17 CYP2E1 messenger RNA levels in different</p> <p>18 regions of the brain.</p> <p>19 I don't dispute -- so there's</p> <p>20 no comparison with the liver here. This is a</p> <p>21 critical point. When they say -- when he</p> <p>22 says that red indicates higher expression and</p> <p>23 green indicates lower expression, that's just</p> <p>24 relative to other parts of the brain.</p> <p>25 Again, I've not disputed that</p>	<p style="text-align: right;">Page 336</p> <p>1 So I wouldn't necessarily say</p> <p>2 that it's one-fifth of what's in the liver.</p> <p>3 It depends on the study you're looking at,</p> <p>4 the conditions of the study and so on.</p> <p>5 I would add, though, that it's</p> <p>6 still millimole per liter concentrations. As</p> <p>7 I said before, that's quite high. There's</p> <p>8 not a lot in the body that exists in</p> <p>9 millimole per liter concentrations.</p> <p>10 Certainly you don't get acetaminophen at</p> <p>11 millimole per liter concentrations after</p> <p>12 therapeutic doses, and since NAPQI -- only a</p> <p>13 small portion of the acetaminophen is</p> <p>14 converted to NAPQI, you definitely don't get</p> <p>15 millimole per liter concentrations of NAPQI.</p> <p>16 So it's plenty of glutathione,</p> <p>17 what's been reported is -- should be plenty</p> <p>18 to detoxify NAPQI.</p> <p>19 MR. JANUSH: Move to strike as</p> <p>20 nonresponsive.</p> <p>21 Doctor, I had only asked you if</p> <p>22 you agreed the brain's glutathione</p> <p>23 capacity is only one-fifth as compared</p> <p>24 to the liver, so everything after that</p> <p>25 answer, I move to strike.</p>
<p style="text-align: right;">Page 335</p> <p>1 there may be some P450 in the brain. What my</p> <p>2 report shows is that it's a negligible amount</p> <p>3 that's far, far lower than what's in the</p> <p>4 liver. And we know that in the liver, with</p> <p>5 very high CYP2E1 levels, you don't get</p> <p>6 clinically significant liver injury at</p> <p>7 therapeutic doses.</p> <p>8 So if you have less than that</p> <p>9 in the brain, there's just no reason to think</p> <p>10 that therapeutic doses would have any effect</p> <p>11 there either.</p> <p>12 Q. Do you agree that the brain's</p> <p>13 glutathione capacity is only one-fifth as</p> <p>14 compared to the liver?</p> <p>15 A. Most reports that I have</p> <p>16 seen -- so this is a somewhat complicated</p> <p>17 question because the amount of glutathione in</p> <p>18 an organ at any one time can depend on</p> <p>19 multiple factors.</p> <p>20 Generally speaking, what has</p> <p>21 been reported is that the levels are around 1</p> <p>22 to 2, sometimes 3 millimole per liter in the</p> <p>23 brain. The liver, depending on what study</p> <p>24 you look at, it's reported anywhere between 5</p> <p>25 and 10 millimole per liter in the brain.</p>	<p style="text-align: right;">Page 337</p> <p>1 Moving to my next question.</p> <p>2 BY MR. JANUSH:</p> <p>3 Q. Have you read Dr. Louie's</p> <p>4 rebuttal report?</p> <p>5 A. I have.</p> <p>6 Q. Incidentally, do you recall</p> <p>7 Dr. Louie citing to the Nuttall article, The</p> <p>8 impact of therapeutic doses of paracetamol on</p> <p>9 serum total antioxidant capacity?</p> <p>10 A. I vaguely recall this, his</p> <p>11 reference to it in the study.</p> <p>12 Q. In your report, you did not</p> <p>13 address the Nuttall publication, right, which</p> <p>14 studied the impact of therapeutic doses of</p> <p>15 acetaminophen taken over a period of time on</p> <p>16 serum total antioxidant capacity?</p> <p>17 A. I don't recall if I considered</p> <p>18 it or not.</p> <p>19 Q. Do you know why you didn't</p> <p>20 address it?</p> <p>21 A. At the time, presumably, if I</p> <p>22 saw it, I deemed it irrelevant.</p> <p>23 Q. In your entire report, did you</p> <p>24 address that the brain has a lower</p> <p>25 glutathione capacity than does the liver?</p>

<p style="text-align: right;">Page 338</p> <p>1 A. Okay. When you say 2 "glutathione capacity," we need to be real 3 careful about what we mean there. I have 4 described the glutathione concentrations in 5 the brain from multiple studies, and I've 6 also stated what a typical range of 7 glutathione concentrations in the liver are. 8 Q. I'm talking about the 9 protective capacity against toxins. Did you 10 address that the brain has a lower 11 glutathione capacity than does the liver? 12 A. As I've stated, in general -- I 13 don't believe I've said it has a lower 14 glutathione capacity. Glutathione 15 concentrations in the brain are typically in 16 the range of 1 to 3 millimole per liter; 17 liver is typically in the range of 5 to 10 18 millimole per liter, based on most studies 19 that I've seen. 20 Q. Moving on to paragraph 49, 21 which is at page 42 of your report, you 22 address... 23 I apologize, I've lost my spot. 24 This is what happens when you're up for 25 30 hours straight. I'm going back to 40,</p>	<p style="text-align: right;">Page 340</p> <p>1 have anything to do with acetaminophen? 2 A. Well, again, I wasn't citing it 3 to support a statement about acetaminophen. 4 I'm citing it to show that there's 5 glutathione present in the brain at a pretty 6 high concentration, but no, it didn't address 7 acetaminophen. 8 Q. Cooper et al., 1980. This is a 9 case where the adult rats were decapitated, 10 and 30 minutes of total decapitation -- 11 30 minutes following total decapitation, 12 decreased total glutathione. 13 Do you remember that? 14 A. My primary interest in that 15 study was in the control rat levels, since 16 that's what's relevant here. But if you want 17 to produce the study, I'd be happy to look 18 through it. 19 Q. I don't. 20 Did the study have anything to 21 do with acetaminophen? 22 A. My response is the same as the 23 one above. I'm not citing it to say anything 24 about acetaminophen. I'm citing it because 25 it shows that there's pretty high</p>
<p style="text-align: right;">Page 339</p> <p>1 forgive me, page 40. Studies of Glutathione 2 in the Brain. 3 THE WITNESS: Do you mind if we 4 took a break? I need to use the 5 restroom. 6 MR. JANUSH: Yeah, no problem 7 at all. 8 THE VIDEOGRAPHER: We're going 9 off record. The time is 4:34. 10 (Recess taken, 4:34 p.m. to 11 4:43 p.m. CDT) 12 THE VIDEOGRAPHER: We are going 13 back on the record. The time is 4:43. 14 BY MR. JANUSH: 15 Q. Going to page 40 of your 16 report, starting with the case of -- the 17 publication Griffith and Meister. Here we're 18 addressing studies of glutathione in the 19 brain that you address at paragraph 49, 20 beginning on page 39. 21 Are you with me? 22 A. Yes. 23 Q. Griffith and Meister, you 24 address that they found glutathione present 25 in the normal adult mouse. Did this study</p>	<p style="text-align: right;">Page 341</p> <p>1 concentrations of glutathione present in the 2 brain. 3 Q. Pileblad and Magnusson, 1988, 4 rats were anesthetized with pentobarbital and 5 polyethylene cannulae were implanted into 6 each ventricle. And one to two days later, 7 L-Buthionine-sulfoximine was administered 8 intracerebroventricularly through cannulae. 9 And the brain content of GSH was determined 10 by high-performance liquid chromatography 11 with electrochemical detection using N-acetyl 12 cysteine as internal standard. 13 Now, do you remember that it 14 was following a dose of L-Buthionine, a 15 maximal depletion of GSH was seen in the 16 cortex and brain stem? Do you remember that 17 in this study? 18 A. Again, my interest in this 19 study is the control levels, not the levels 20 of treatment with buthionine sulfoximine. 21 But just in case I slip into that language, 22 just to be clear, I typically refer to that 23 as BSO, so BSO. 24 That's -- that's not surprising 25 that it would deplete glutathione in the</p>

<p style="text-align: right;">Page 342</p> <p>1 brain because it's an inhibitor of the</p> <p>2 rate-limiting enzyme in glutathione</p> <p>3 synthesis. But again, my interest here is in</p> <p>4 the control levels.</p> <p>5 Q. Where do you say that in your</p> <p>6 report? I didn't see that.</p> <p>7 A. It says normal adult rat brain,</p> <p>8 so not BSO-depleted at all.</p> <p>9 Q. Got it. Okay.</p> <p>10 Jain et al., here newborn rats,</p> <p>11 36 to 48 hours old, were treated with</p> <p>12 buthionine sulfoximine or saline control for</p> <p>13 three or nine days, and measured glutathione</p> <p>14 in the brain.</p> <p>15 What was your interest in</p> <p>16 studying this -- this particular publication?</p> <p>17 A. Again, same thing, I was</p> <p>18 interested in the control levels that they</p> <p>19 reported, so the saline-treated animals. I</p> <p>20 just mentioned that they were -- those were</p> <p>21 saline treated because -- you know, in</p> <p>22 case -- just full disclosure, I guess, of the</p> <p>23 way the animals were handled.</p> <p>24 But saline treatment doesn't do</p> <p>25 anything. That's why it's a vehicle control.</p>	<p style="text-align: right;">Page 344</p> <p>1 information at hand.</p> <p>2 Q. Well, I'm addressing numbers</p> <p>3 here, and so are you, and I'm addressing</p> <p>4 standard of error.</p> <p>5 So if you are comparing 1.4 in</p> <p>6 terms of the measurement found in human adult</p> <p>7 brains as against the 2.5 and 2.3 measurement</p> <p>8 of glutathione concentrations in terms of</p> <p>9 millimoles per kilogram found in the babies'</p> <p>10 brains, mathematically speaking and from a</p> <p>11 scientific standpoint, if there's a</p> <p>12 standard -- a margin of error as high as .9,</p> <p>13 plus or minus, that may render the difference</p> <p>14 immaterial, right?</p> <p>15 A. I cannot say based on the</p> <p>16 information that's in here. You would need a</p> <p>17 number of additional pieces of information</p> <p>18 such as what test -- what statistical test</p> <p>19 was done, how many animals they used in each</p> <p>20 group, what was the standard error --</p> <p>21 preferably standard deviation on the other</p> <p>22 value that we're comparing with, not just</p> <p>23 that 0.9.</p> <p>24 In addition to that, I'm not a</p> <p>25 professional biostatistician. I typically</p>
<p style="text-align: right;">Page 343</p> <p>1 It's biologically inert.</p> <p>2 Q. So I'm going to jump forward to</p> <p>3 the Kreis publication, which used magnetic</p> <p>4 resonance spectroscopy approach to measure</p> <p>5 glutathione concentrations in the brains of</p> <p>6 human infants delivered preterm or shortly</p> <p>7 after birth.</p> <p>8 And you address, with respect</p> <p>9 to this, that they reported averages --</p> <p>10 average values of 2.5 and 2.3 millimoles per</p> <p>11 kilogram for preterm and term babies,</p> <p>12 respectively, and that these values were</p> <p>13 higher than the reported concentration of 1.4</p> <p>14 measured in human adult brains.</p> <p>15 Did you notice that there was a</p> <p>16 standard of error on that Table 1A in Kreis</p> <p>17 of plus or minus .9?</p> <p>18 A. I don't recall off the top of</p> <p>19 my head what the standard error was.</p> <p>20 Q. So if, hypothetically, there's</p> <p>21 a standard of error of plus or minus .9, is</p> <p>22 there a meaningful difference between 2.5,</p> <p>23 2.3, and by contrast, 1.4?</p> <p>24 A. I would have to have way more</p> <p>25 data to make that assessment, way more</p>	<p style="text-align: right;">Page 345</p> <p>1 involve professional biostatisticians in my</p> <p>2 work.</p> <p>3 Q. But you're using numbers and</p> <p>4 citing them to demonstrate differences</p> <p>5 between an adult brain, measured for</p> <p>6 glutathione concentration, and the brains of</p> <p>7 human infants delivered preterm or shortly</p> <p>8 after birth, also measured for glutathione</p> <p>9 concentration, and nowhere do you reference</p> <p>10 that there was a margin of error of plus or</p> <p>11 minus .9.</p> <p>12 MR. COHEN: Object to the form.</p> <p>13 BY MR. JANUSH:</p> <p>14 Q. Right?</p> <p>15 MR. COHEN: Object to the form.</p> <p>16 I think without showing him the study,</p> <p>17 this testimony is unfair.</p> <p>18 But go ahead.</p> <p>19 A. Yeah --</p> <p>20 BY MR. JANUSH:</p> <p>21 Q. Well, assume that I'm not</p> <p>22 lying --</p> <p>23 MR. COHEN: I'm not accusing</p> <p>24 you of lying. I'm just talking about</p> <p>25 fairness.</p>

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1 BY MR. JANUSH:
 2 Q. -- and that I'm just trying to
 3 move on quickly and not show you a table just
 4 to have time wasted.
 5 If, hypothetically, there's a
 6 standard of error, a margin of error of plus
 7 or minus .9 that was not addressed by you,
 8 that may -- that comprises a meaningful
 9 difference in -- and impacts the conclusion
 10 you reach regarding the differences between
 11 adults' and babies' glutathione measurements,
 12 right?
 13 MR. COHEN: Objection, form.
 14 MR. JANUSH: I can ask it more
 15 clean.
 16 A. It was quite a long question.
 17 Would you mind --
 18 BY MR. JANUSH:
 19 Q. I'll break it down.
 20 .9, plus or minus, margin of
 21 error should not have been ignored by you
 22 when assessing the Kreis publication if that
 23 margin of error existed between adults and
 24 babies, true?
 25 MR. COHEN: Objection, form.

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1 A. Again, to make any statement
 2 about the statistical significance of that
 3 difference between 2.3, 2.5 and 1.4, I would
 4 need far more information.
 5 Since I noted it here and
 6 specifically said it was higher, I assumed
 7 the authors did statistical testing and
 8 provided a result for that.
 9 BY MR. JANUSH:
 10 Q. Do you have 821 in front of
 11 you?
 12 A. 821?
 13 Q. Brzezinski, the Catalytic
 14 Activity and Quantitation of Cytochrome P-450
 15 2E1 in Prenatal Brain?
 16 A. I have it here, yes.
 17 Q. And when we look at Figure 3,
 18 aren't we looking at a western blot of CYP2E1
 19 protein in the prenatal human brain?
 20 A. No. This is not a western
 21 blot. This is an RNA protection assay which
 22 quantifies messenger RNA.
 23 Q. Oh, my apologies. That's
 24 the -- I can't even see right now. That's
 25 the ribonuclease protection assay.

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1 The immunoblot analysis is
 2 Figure 1.
 3 Do you see that?
 4 A. I do.
 5 Q. And this is analysis of CYP2E1
 6 content in microsome from prenatal human
 7 brain and adult rat tissues, right?
 8 A. Yes, that's the title of the
 9 figure.
 10 Q. So this is -- this is
 11 showing -- well, why don't you tell me.
 12 What is meaningful about this
 13 to you?
 14 A. So what's meaningful about this
 15 to me, what's particularly notable, is that
 16 it actually shows that the adult rat brain
 17 has a much lower CYP2E1 than the liver.
 18 Q. What does it show you with
 19 respect to the human brain?
 20 A. Well, again, it shows me
 21 that -- as I've said, I'm not disputing there
 22 might be some -- a little bit of CYP2E1 in
 23 the brain, including the fetal brain; it's
 24 just a negligible amount. So this is
 25 consistent with that. They've apparently

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1 detected a little bit of CYP2E1 in the brain,
 2 but again, it's lower than what they've
 3 detected -- much lower than what they've
 4 detected in the rat adult liver.
 5 Q. And they've detected it in both
 6 the prenatal human brain at fetal -- let's
 7 see. I'm trying to compare it. It's hard
 8 through this reading.
 9 I mean, what is clear is that
 10 there's a predominant band of immunoactive
 11 protein visible in each lane of the sample
 12 corresponding to CYP2E1, right?
 13 A. I don't know what you mean by
 14 predominant.
 15 Q. Well, that's what the authors
 16 noted, right?
 17 A. I don't recall the exact
 18 wording that they used.
 19 Q. Go to the bottom of Figure 1.
 20 The sentence states: A predominant band of
 21 immunoreactive protein is visible in each
 22 lane of sample and standard corresponding to
 23 CYP2E1.
 24 A. Again, the data show that the
 25 levels are far lower than in the rat adult

<p style="text-align: right;">Page 350</p> <p>1 liver. They only loaded 10 nanograms, 2 nanograms of protein for the rat liver. 3 They've loaded microgram quantities, so on 4 the order of a thousand-fold greater for the 5 brain samples. 6 And despite adding a 7 thousand-fold more protein, the levels still 8 look a bit lower. When you take into 9 consideration how much they loaded, it's far 10 lower. 11 Q. Did the authors conclude that a 12 minimal band exists or a predominant band of 13 visible CYP2E1 protein, immunoreactive 14 protein exists? 15 A. What they stated, if you look 16 in the second paragraph up from that figure, 17 the second-to-last sentence, it says their 18 conclusion about that figure. 19 The enzyme was present at 20 approximately 1.6 micrograms per milligram 21 microsomal protein, similar to the amount in 22 adult rat brain and about 150-fold less than 23 the amount measured in the rat adult liver. 24 Q. Not 1,000-fold less as you've 25 addressed in your expert report, right?</p>	<p style="text-align: right;">Page 352</p> <p>1 acetaminophen-treated pregnant rats gave 2 birth to offspring that were deemed to have 3 neurological development -- developmental 4 issues which the authors corresponded to 5 increased oxidative stress in the brain? 6 A. I don't recall exactly what the 7 authors concluded. I would need to see the 8 study in front of me. 9 In addition, I can't comment on 10 anything about neurobehavioral outcomes. 11 (Whereupon, Deposition 12 Exhibit P825, Perinatal exposure to 13 paracetamol: Dose and sex-dependent 14 effects in behaviour and brain's 15 oxidative stress markers in progeny, 16 by Rigobello et al., was marked for 17 identification.) 18 BY MR. JANUSH: 19 Q. You understand pregnant women 20 aren't suing because their fetuses were 21 exposed to Tylenol and that they had liver 22 damage, right? 23 MR. COHEN: Objection, form. 24 A. My understanding of the 25 plaintiffs' complaint is that they are --</p>
<p style="text-align: right;">Page 351</p> <p>1 A. Again, I've explained the way I 2 came to that thousand-fold number. I cited 3 16 different studies, not just one. This was 4 one of the studies that I included in that 5 calculation. 6 Those 16 different studies 7 provide 12 numbers comparing the levels in 8 brain and liver, and if you average those 12 9 numbers, it actually comes out to more than a 10 thousand-fold less than the brain compared to 11 the liver. 12 So again, I was actually being 13 conservative in my -- the number that I gave 14 in my report. 15 Q. At paragraph 51 of your report, 16 you address that at least two studies have 17 demonstrated that chronic exposure to 18 acetaminophen during early in utero 19 development has no effect on brain 20 glutathione levels later in life. And you 21 address the Klein publication and Rigobello 22 2021, right? 23 A. Correct. 24 Q. With respect to Rigobello, do 25 you agree that Rigobello 2021 concluded that</p>	<p style="text-align: right;">Page 353</p> <p>1 they claim that they -- their offspring 2 suffered some neurodevelopmental adverse 3 effects from in utero acetaminophen exposure. 4 So it's not about the liver. 5 But again, we -- we used the liver as a 6 framework, and that's due in large part to 7 the fact that the plaintiffs' experts used 8 the liver as a reference and framework. 9 BY MR. JANUSH: 10 Q. I'm just going to jump straight 11 to the conclusion at page 5, paragraph 5, 12 first three sentences only, and I'm going to 13 move on. 14 In conclusion, our study 15 describes behavioral and brain oxidative 16 stress parameters altered in infant rats 17 after gestational and lactational exposure to 18 human-relevant doses of PAR. 19 PAR is paracetamol, right? 20 A. Yes. I disagree strongly with 21 that conclusion, by the way, for the record. 22 I'm more than happy to explain why. 23 MR. JANUSH: Sorry, this is 24 Exhibit P825; and it's Rigobello, 25 titled Perinatal exposure to</p>

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1 paracetamol: Dose and sex-dependent
 2 effects in behaviour and brain's
 3 oxidative stress markers in progeny.
 4 BY MR. JANUSH:
 5 Q. But in this case, it's your
 6 hypothesis that there's adequate glutathione
 7 in the brain to accommodate any NAPQI
 8 production in the fetus, right?
 9 MR. COHEN: Object to form.
 10 A. I'm not sure what you mean by
 11 "in this case." Are you referring to this
 12 study in general?
 13 BY MR. JANUSH:
 14 Q. No, in general, in this
 15 litigation. I mean, you're here as an expert
 16 for the litigation, not as an expert on this
 17 particular piece of published literature,
 18 right?
 19 A. I'm quite confident that
 20 there's sufficient -- if -- if any NAPQI
 21 could form in the brain after exposure to
 22 acetaminophen, I'm quite confident that
 23 there's enough glutathione to scavenge it.
 24 However, there's data showing that you don't
 25 get NAPQI in the brain, so it's kind of moot.

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1 Q. Do you agree that the findings
 2 of Brzezinski that CYP2E1 was found in the
 3 brain of rats are consistent with what
 4 Rigobello has found using subtoxic
 5 acetaminophen doses of 35 milligrams per
 6 kilogram or 350 milligrams per kilogram?
 7 A. I have a number of comments
 8 about that. Their finding -- and I believe
 9 that was Brzezinski. Let me just
 10 double-check so I'm not misstating. Right.
 11 Okay.
 12 Again, you remember in
 13 Brzezinski, they reported 150-fold lower
 14 levels of CYP2E1 in the brain. The lack of
 15 consistent reproducible effects on
 16 glutathione, for example, in this study is
 17 consistent with very low P450s in the brain,
 18 as Brzezinski reported.
 19 Furthermore, this study can't
 20 be used really to say anything about NAPQI
 21 formation in the brain, and that's because,
 22 if I remember correctly, they're looking at
 23 22 days, at least, after exposure. There
 24 would be no acetaminophen or NAPQI present,
 25 so any effect on glutathione would be due to

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1 something else.
 2 Q. I'm going to jump to Studies of
 3 NAPQI Surrogates in the Brain and address the
 4 Fischer study that you cite. And that's on
 5 page 44 of your report.
 6 A. Uh-huh.
 7 Q. Dr. McGill, didn't Fischer use
 8 older liquid chromatography method that has a
 9 limit of detection in the 50 to 100 nanomolar
 10 range?
 11 A. They used a method with
 12 radiolabeled acetaminophen, so they're
 13 counting radioactivity. I don't recall if
 14 there was any HPLC separation step or not
 15 before that.
 16 This was an approach where you
 17 measure protein binding by -- you have a
 18 radiolabeled drug like acetaminophen. You
 19 inject the animals, harvest the tissue, and
 20 then basically -- basically wash the tissue
 21 to get rid of anything that's not tightly
 22 bound to it.
 23 And then you measure the
 24 radioactivity that's -- I believe, if I
 25 remember correctly, that's how they did this

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1 study.
 2 Radioactivity is pretty --
 3 quite sensitive.
 4 Q. If Fischer did use older liquid
 5 chromatography, as I've said, with a limit --
 6 older chromatography would have a limit of
 7 detection in the 50 to 100 nanomolar range;
 8 wouldn't that be right?
 9 A. I mean, liquid chromatography,
 10 first of all, characterizing it as older is
 11 odd. We do quite a lot of liquid
 12 chromatography today, and liquid
 13 chromatography, there are many different
 14 kinds of liquid chromatography.
 15 Q. In 1981?
 16 A. Oh, yeah, yeah, yeah. Liquid
 17 chromatography is one of the oldest methods
 18 to separate small molecules in samples. It's
 19 been around probably over a century would be
 20 my guess.
 21 Q. What I'm getting at is: If --
 22 if older liquid chromatography from 1981 had
 23 a limit detection in the 50 to 100 nanomolar
 24 range, that might not be able to detect
 25 levels of all APAP conjugates in the brain,

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1 right?

2 A. Levels of -- I -- are you

3 asking about acetaminophen-protein

4 conjugates?

5 Q. I am.

6 A. Just to make that more clear.

7 Off -- I mean, off the top of

8 my head, I can't say. I also don't -- yeah.

9 Again, radioactivity is -- it's a very, very

10 sensitive approach. It's so sensitive it's

11 prone to noise.

12 Q. Turning to the Bien study that

13 you cite. Bien used a simpler colorimetric

14 assay that has lower sensitivity than more

15 modern methods do to study GSH; isn't that

16 right?

17 A. No, that's not correct. One of

18 the best methods available to measure

19 glutathione is what's called the Tietze

20 method. It's what I use in my laboratory.

21 Depending on how you set up the

22 assay, it can be extremely sensitive. It's

23 certainly -- I mean, I use it all the time in

24 my studies with acetaminophen to look at

25 glutathione depletion. It's certainly

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1 sensitive enough for that purpose.

2 Q. Is the Tietze method using --

3 using colorimetric assay?

4 A. Yes.

5 Q. And you disagree that it has

6 lower sensitivity than more modern methods to

7 study GSH?

8 A. Yeah. I also don't think

9 sensitivity is an issue here, right, because

10 you have -- sensitivity is important when

11 you're trying to measure something that's

12 very, very low abundance, right? But again,

13 as I've stated, glutathione has presence in

14 very high concentrations, millimole per

15 liter. It's quite high for the body.

16 Sensitivity is not an issue.

17 But whether it's an issue or

18 not, these colorimetric methods can

19 absolutely be extremely sensitive.

20 Q. Turning to Micheli (1993).

21 Were rats dosed with 3,000 milligrams per

22 kilogram?

23 A. That's my recollection of this

24 study.

25 Q. And do you claim the authors

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1 reported only minor reductions of

2 glutathione, 14-24%, in various regions of

3 the brain?

4 A. Again, that's my recollection

5 of the data.

6 Q. But didn't the authors in

7 Micheli address, quote, from a physiologic

8 standpoint, a 20 to 30% decrease of GSH

9 levels is considered significant and able to

10 start a reversible or irreversible toxic

11 process?

12 Do you remember reading that?

13 A. I don't recall if they used

14 those exact words. I'd be happy to see the

15 report if you want to produce it.

16 Q. I don't.

17 A. In addition -- in addition, I

18 disagree with that. We know again, if you

19 look at my 2013 study, for example, in the

20 liver, at 15 milligram per kilogram, we

21 saw -- I don't remember the exact amount,

22 probably 15, 20% loss of glutathione in the

23 liver, there was no evidence of liver injury.

24 At the 75-milligram per

25 kilogram dose, there was almost complete loss

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1 of glutathione in the liver. There was still

2 no liver injury at that dose.

3 So no, that statement is

4 categorically incorrect.

5 Q. So you disagree with the

6 Micheli authors who wrote those words?

7 A. Yeah. In addition, they're

8 only seeing this at the 3,000-milligram per

9 kilogram dose, which again, has no relevance

10 to maternal ingestion of therapeutic doses.

11 Q. But again, you yourself have

12 recognized that rats have to be dosed

13 significantly higher because they're poorer

14 than mice in terms of animal study objects,

15 study animals?

16 A. I've also explained that these

17 doses -- that the rat model has no relevance

18 to human therapeutic use or whether --

19 talking about large doses or not. These very

20 large doses in rats result in these millimole

21 per liter plasma concentrations of

22 acetaminophen which you never see with

23 therapeutic use of acetaminophen. Those are

24 overdose concentrations. That's what you

25 would see in an overdose patient.

<p>Page 362</p> <p>1 In fact, it's higher than what</p> <p>2 you see sometimes in acetaminophen overdose</p> <p>3 patients.</p> <p>4 Q. At paragraph 56, where you</p> <p>5 address maternal use of therapeutic doses of</p> <p>6 acetaminophen and oxidative stress, this is</p> <p>7 the portion of your report where you address</p> <p>8 plaintiffs' claims relative to oxidative</p> <p>9 stress as a potential mechanism of action</p> <p>10 that leads to adverse fetal</p> <p>11 neurodevelopmental outcomes, right?</p> <p>12 A. Yes. Well, I'm sorry, let me</p> <p>13 rephrase that.</p> <p>14 This is the portion of my</p> <p>15 report where I address the issue of whether</p> <p>16 or not there's evidence that oxidative stress</p> <p>17 occurs in the brain with maternal use of</p> <p>18 therapeutic doses of acetaminophen.</p> <p>19 Q. And you also address that no</p> <p>20 studies have been presented by plaintiff</p> <p>21 experts demonstrating that -- right, I mean,</p> <p>22 I'm going to quote it exactly.</p> <p>23 A. Uh-huh.</p> <p>24 Q. Demonstrating that therapeutic</p> <p>25 doses of acetaminophen caused oxidative</p>	<p>Page 364</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. Do you agree that cell culture</p> <p>3 lines of evidence are relevant and should be</p> <p>4 considered in a true weight of evidence</p> <p>5 analysis?</p> <p>6 MR. COHEN: Object to the form.</p> <p>7 A. A formal weight of evidence</p> <p>8 analysis is not common in my field, so I</p> <p>9 can't comment on that.</p> <p>10 In addition, the cell culture</p> <p>11 studies described by Posadas are irrelevant</p> <p>12 for human therapeutic use of acetaminophen.</p> <p>13 They have used, again, 0.5- to 2-millimole</p> <p>14 per liter concentrations for very long</p> <p>15 durations of exposure in those cell culture</p> <p>16 studies. That absolutely does not mimic</p> <p>17 human therapeutic exposure to acetaminophen.</p> <p>18 BY MR. JANUSH:</p> <p>19 Q. By the way, let me go back and</p> <p>20 ask you something that's sticking in my mind.</p> <p>21 You addressed that the rat</p> <p>22 model has no relevance here, but you</p> <p>23 repeatedly included the rat model and rat</p> <p>24 model studies in your report, right?</p> <p>25 A. I discuss --</p>
<p>Page 363</p> <p>1 stress in the human embryonic/fetal brain.</p> <p>2 Instead, plaintiff experts either fail to</p> <p>3 cite studies to support this hypothesis or</p> <p>4 rely on studies that use excessive doses or</p> <p>5 concentrations of acetaminophen.</p> <p>6 Right?</p> <p>7 A. Correct.</p> <p>8 Q. Do you agree that it is</p> <p>9 ethically impossible to measure oxidative</p> <p>10 stress in the human embryonic/fetal brain and</p> <p>11 then follow up later to see if that test</p> <p>12 subject has neurological --</p> <p>13 neurodevelopmental disorders?</p> <p>14 MR. COHEN: Objection to form.</p> <p>15 A. Well, again, I am not an</p> <p>16 ethicist. I can't comment on ethics. That's</p> <p>17 not what I'm here to discuss.</p> <p>18 BY MR. JANUSH:</p> <p>19 Q. But that testing would result</p> <p>20 in the death of the embryo and fetus,</p> <p>21 wouldn't it?</p> <p>22 MR. COHEN: Objection to form.</p> <p>23 A. I'm not a physician. I don't</p> <p>24 know what kind of sampling is possible</p> <p>25 without harming the child.</p>	<p>Page 365</p> <p>1 MR. COHEN: Object to the form.</p> <p>2 Go ahead.</p> <p>3 A. I discuss them in my report</p> <p>4 because, again, my report is, in part, a</p> <p>5 response to the plaintiffs' experts' reports</p> <p>6 who discussed some of these studies -- who</p> <p>7 discussed these studies.</p> <p>8 BY MR. JANUSH:</p> <p>9 Q. Do you have any methodology on</p> <p>10 oxidative stress?</p> <p>11 A. Can you --</p> <p>12 Q. In terms of how and why</p> <p>13 oxidative stress would not be created by</p> <p>14 virtue of prenatal exposure in utero to</p> <p>15 acetaminophen.</p> <p>16 MR. COHEN: Objection, form.</p> <p>17 A. Again, we're working within the</p> <p>18 framework of what happens in the liver as</p> <p>19 established by the plaintiffs' experts.</p> <p>20 In the liver, you do not get</p> <p>21 oxidative stress after acetaminophen exposure</p> <p>22 without NAPQI formation. There's evidence --</p> <p>23 we know that you don't get NAPQI formation in</p> <p>24 the brain after acetaminophen overdose --</p> <p>25 overdose, much less therapeutic doses.</p>

<p style="text-align: right;">Page 366</p> <p>1 BY MR. JANUSH:</p> <p>2 Q. In reaching your conclusion,</p> <p>3 why did you not address the publication by</p> <p>4 Beck which found that even at the lowest dose</p> <p>5 of 125 milligrams per kilogram APAP given to</p> <p>6 rats, thiols appeared to be almost absent</p> <p>7 altogether in embryos studied, suggesting</p> <p>8 that GSH was depleted?</p> <p>9 MR. COHEN: Objection, form.</p> <p>10 A. First of all, if you're going</p> <p>11 to ask questions about the study, I'd like to</p> <p>12 see it.</p> <p>13 And again, I would note,</p> <p>14 125 milligram per kilogram -- milligrams per</p> <p>15 kilogram is not a human-relevant dose, not a</p> <p>16 therapeutic dose.</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. It's a very small dose given to</p> <p>19 rats, isn't it?</p> <p>20 A. Again, this gets into the issue</p> <p>21 of sub-hepatotoxic and therapeutic are not</p> <p>22 interchangeable terms by any means.</p> <p>23 I also, off the top of my head,</p> <p>24 don't know what plasma concentrations that</p> <p>25 particular dose results in. It's likely much</p>	<p style="text-align: right;">Page 368</p> <p>1 Q. We were hoping you would have</p> <p>2 reviewed it in your report, Dr. McGill.</p> <p>3 MR. COHEN: Objection to the</p> <p>4 statement. That's not a question.</p> <p>5 That sounds like a lecture.</p> <p>6 A. Again, the dose that you</p> <p>7 mentioned was far higher than therapeutic</p> <p>8 doses in humans.</p> <p>9 BY MR. JANUSH:</p> <p>10 Q. What do you believe an</p> <p>11 analgesic dose of acetaminophen is for a</p> <p>12 laboratory mouse?</p> <p>13 A. I haven't reviewed the study</p> <p>14 on -- I haven't reviewed all the literature</p> <p>15 on analgesic doses of acetaminophen in mice.</p> <p>16 I can't really comment on that.</p> <p>17 But the question is not</p> <p>18 necessarily about what's an analgesic dose in</p> <p>19 a rodent. The question is do the exposure</p> <p>20 levels in those models mimic exposure levels</p> <p>21 in humans. When you're giving such large</p> <p>22 doses, they absolutely don't.</p> <p>23 Q. What do you believe is the</p> <p>24 appropriate dose of acetaminophen for a</p> <p>25 laboratory mouse?</p>
<p style="text-align: right;">Page 367</p> <p>1 higher than human therapeutic concentrations.</p> <p>2 Q. Why did you -- sorry.</p> <p>3 Why did you fail to address the</p> <p>4 Baker et al., 2023 mouse study in which the</p> <p>5 scientists, including Dr. Pearson, gave</p> <p>6 pregnant mice 150 milligrams per kilogram and</p> <p>7 showed evidence for inflammatory and</p> <p>8 oxidative stress in the brain of the</p> <p>9 APAP-exposed neonatal mice using a dose that</p> <p>10 is therapeutic for mice?</p> <p>11 MR. COHEN: Objection to the</p> <p>12 form.</p> <p>13 A. Again, I'd need to see the</p> <p>14 study in front of me to assess it. I'm happy</p> <p>15 to discuss it if you can produce a copy of</p> <p>16 it.</p> <p>17 BY MR. JANUSH:</p> <p>18 Q. I'm not producing a copy, but</p> <p>19 it's on page 3 of your materials referred</p> <p>20 list or your reference list, so --</p> <p>21 A. Yeah, I don't recall what their</p> <p>22 claimed evidence for oxidative stress is. I</p> <p>23 would need to review that if you want me to</p> <p>24 make a meaningful statement about it.</p> <p>25 Again --</p>	<p style="text-align: right;">Page 369</p> <p>1 A. Appropriate dose to achieve --</p> <p>2 sorry.</p> <p>3 MR. COHEN: Objection, form.</p> <p>4 Go ahead.</p> <p>5 A. Appropriate dose to achieve</p> <p>6 what?</p> <p>7 BY MR. JANUSH:</p> <p>8 Q. To test for inflammatory and</p> <p>9 oxidative stress in the brain of exposed</p> <p>10 neonatal mice.</p> <p>11 A. Well, then I --</p> <p>12 Q. You've criticized Dr. Baker and</p> <p>13 Dr. Pearson and their study group regarding</p> <p>14 150 milligrams per kilogram. So if you were</p> <p>15 designing that study, what would you have</p> <p>16 done?</p> <p>17 MR. COHEN: Objection, form.</p> <p>18 A. If -- if I were designing a</p> <p>19 study to look at potential oxidative stress</p> <p>20 in the brain with acetaminophen, the dose</p> <p>21 that I would use is 14 to 15 milligrams per</p> <p>22 kilogram.</p> <p>23 BY MR. JANUSH:</p> <p>24 Q. AM404, paragraph 62, you</p> <p>25 address that: AM404 has been described as</p>

<p style="text-align: right;">Page 370</p> <p>1 having a potential role in acetaminophen's 2 mechanism of action for reducing pain and 3 lowering body temperature. The proposed CNS 4 pathways for the drug's analgesic effects 5 include endocannabinoid, serotonergic, and 6 nitric oxide pathways. The presence of AM404 7 in central nervous system and its potential 8 effects was not described until recently. A 9 limited number of studies have examined 10 whether the biological effects of 11 acetaminophen can be mediated by AM404, and 12 only one study has examined the production of 13 AM404 after acetaminophen use in humans.</p> <p>14 Dr. McGill, isn't it true that 15 AM404 literature is actually quite extensive 16 and dates back to at least 2004, predating 17 even the EPI?</p> <p>18 MR. COHEN: Object to the form.</p> <p>19 A. You asked a very broad question 20 about AM404 literature. I don't know when 21 the first mention of AM404 in the literature 22 is. The data on acetaminophen and AM404, of 23 which I'm aware, is what I would consider 24 relatively recent, within the last -- I mean, 25 it's hard to give a range for recent -- I</p>	<p style="text-align: right;">Page 372</p> <p>1 sure.</p> <p>2 Q. At paragraph 66, you address 3 that Högestätt et al., 2005, treated rats 4 with 300 milligrams per kilogram of 5 acetaminophen and were able to detect AM404 6 in the brain. However, a dose of 7 300 milligrams per kilogram of acetaminophen 8 results in blood concentrations that vastly 9 exceed concentrations in humans during 10 therapeutic use.</p> <p>11 Do you see that?</p> <p>12 A. Uh-huh. Yes. Sorry.</p> <p>13 Q. And then similarly, in 14 paragraph 66, you also address Mallet, and 15 again, deem that the authors administered 16 rats with an overdose of 300 milligrams per 17 kilogram and tested their tolerance to pain; 18 is that right?</p> <p>19 Let me ask a different 20 question.</p> <p>21 Do you deem -- do you -- 22 despite what we've heard you say on video as 23 you presented about rats and how immune they 24 are to hepatotoxicity, you deem 25 300 milligrams per kilogram for rats to be an</p>
<p style="text-align: right;">Page 371</p> <p>1 don't know, 10, 15 years at most, that I can 2 recall.</p> <p>3 In addition to that, I wouldn't 4 characterize it as a -- at least with respect 5 to AM404 and acetaminophen as "a lot of 6 research." I mean, compared to what? If you 7 look at research on acetaminophen, it's been 8 ongoing for, I mean, since it was synthesized 9 and discovered in the late 1800s. There are 10 tens of thousands of papers on acetaminophen, 11 maybe more.</p> <p>12 BY MR. JANUSH:</p> <p>13 Q. AM404 in sufficient quantities 14 has an analgesic effect; is that right?</p> <p>15 A. I -- that's -- the analgesic 16 effects and that sort of thing is not what I 17 was asked to comment on.</p> <p>18 Q. And AM404 has an analgesic 19 effect because it operates on the central 20 nervous system, doesn't it?</p> <p>21 A. Again, a number of -- well, a 22 number of pathways have been implicated in 23 whatever -- whatever effects AM404 may have. 24 Whether or not it actually acts on the 25 central nervous system, I couldn't say for</p>	<p style="text-align: right;">Page 373</p> <p>1 overdose administration?</p> <p>2 A. Yeah. Yeah, for sure. Again, 3 it results -- we know -- let's just take the 4 Posadas study, which we've already discussed, 5 a lower overdose than 300 -- 250 milligram 6 per kilogram resulted in plasma 7 concentrations of, again, 1 millimole per 8 liter; that is 1,000 micromole per liter.</p> <p>9 Maximum therapeutic plasma 10 concentrations in a human are 100 -- around 11 130 micromole per liter, so it's at least 12 7.6-fold higher plasma concentrations. That 13 has absolutely no relevance to maternal 14 ingestion of therapeutic doses of 15 acetaminophen.</p> <p>16 Q. When you know an animal such as 17 a rat is ten times less susceptible to liver 18 injury than mice, should scientists scale 19 their studies to better test for the 20 potentially injurious outcome they are 21 studying when using rats as test animals?</p> <p>22 A. We've been over the animal 23 equivalent dosing. I've shared my opinion on 24 that.</p> <p>25 We know a lot about</p>

<p style="text-align: right;">Page 374</p> <p>1 acetaminophen. We know the therapeutic 2 plasma concentration. I have no reason to 3 believe that we shouldn't aim for those 4 concentrations in a rat, for the studies -- 5 types of studies that we're discussing 6 related to the brain. 7 Q. Aiming for concentrations of 8 human therapeutic doses in rats leads -- 9 necessarily leads to ignoring that the rat is 10 ten times less susceptible to liver injury 11 than mice, doesn't it? 12 A. No. So again, I have no reason 13 to believe that the brain is more susceptible 14 to -- or excuse me, that the rat brain is 15 less susceptible to acetaminophen. In fact, 16 in general -- I'm sorry, let me start again. 17 I want to make sure I'm saying it correctly. 18 I have no reason to believe 19 that the rat brain is more resistant to 20 acetaminophen as a matter of -- well, I'm 21 sorry. I'm -- I need to rephrase. 22 Essentially, I have no 23 particular reason to believe that we need to 24 adjust the dose to look at that in the brain. 25 Yeah, I mean, the brain in general is</p>	<p style="text-align: right;">Page 376</p> <p>1 that neutralizes the CYP2E1? 2 A. Neutralizes the CYP2E1? 3 MR. COHEN: Object to the form. 4 BY MR. JANUSH: 5 Q. Excuse me, that neutralizes 6 the -- yeah, the CYP2E1. That's exactly what 7 I meant. 8 In other words, you address 9 that there's sufficient glutathione to handle 10 any expression of CYP2E1. Are you assuming 11 that that's a -- there's a perfect solution 12 that -- for the fetus that neutralizes 13 CYP2E1? 14 MR. COHEN: Object to the form. 15 Answer, if you can. 16 A. Right. Again, I'm not saying 17 anything about neutralizing CYP2E1. 18 Glutathione neutralizes or detoxifies NAPQI. 19 BY MR. JANUSH: 20 Q. I meant to say that. I 21 apologize. I've been up for 30 hours 22 straight. I meant to say NAPQI. 23 MR. COHEN: Do you want to 24 reask the question? 25 THE WITNESS: Yeah, please, if</p>
<p style="text-align: right;">Page 375</p> <p>1 obviously resistant to NAPQI formation, 2 right, because we don't see any NAPQI 3 formation in the brain, even with massive 4 overdoses of acetaminophen. And there's very 5 little -- little to no CYP2E1 in the brain. 6 Q. Talking about humans, you do 7 not know the dose of acetaminophen necessary 8 to affect fetal neurodevelopment, right? 9 A. Again, I'm not here to address 10 studies on neurodevelopmental outcomes or 11 things -- I'm not here to address 12 neurodevelopmental outcomes. 13 Q. And you don't know the duration 14 of use at therapeutic doses that would affect 15 fetal neurodevelopment, right? 16 A. Again, I'm not here to address 17 neurodevelopmental outcomes. We know the 18 concentrations and duration of exposure in 19 human -- to acetaminophen in humans at 20 therapeutic doses, and we know that the rat 21 model and that these high doses, whether 22 you're in mice or rats, do not mimic that 23 human exposure. 24 Q. In this case, are you assuming 25 that there's a perfect solution for the fetus</p>	<p style="text-align: right;">Page 377</p> <p>1 you don't mind, I'm sorry. 2 MR. JANUSH: Yeah. 3 BY MR. JANUSH: 4 Q. Do you believe that there's a 5 perfect solution for the fetus that 6 neutralizes NAPQI expression? 7 A. What we know is that you have, 8 number one, very little P450 in the brain 9 relative to liver. My studies described in 10 my report demonstrate that. 11 What we know is that you have 12 glutathione at millimole per liter 13 concentrations in the brain. Again, studies 14 described in my report show that. 15 We also know that in order to 16 have toxicity -- significant clinical liver 17 injury in the liver with acetaminophen, which 18 has far more CYP2E1, you would need an 19 overdose. Therapeutic doses don't cause any 20 injury in the liver, despite having much more 21 CYP2E1 than the brain. 22 So you certainly wouldn't 23 expect that an organ like the brain with 24 much, much less CYP2E1 would be susceptible 25 to injury at therapeutic doses.</p>

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1 I guess I'll stop there.

2 Q. In your report, you mention

3 that your independent research group has been

4 primarily funded by UAMS and by the American

5 Association for the Study of Liver Diseases

6 Foundation, with additional funding from

7 GlaxoSmithKline and Haleon, Bergstrom

8 Nutrition and the Federal Transit Authority.

9 What kinds of research have you

10 performed that was funded by GSK?

11 A. I'm under a contractual

12 obligation not to share the details of those

13 studies, so I can't comment on that, except

14 to say that it's not related to effects on

15 the brain of acetaminophen.

16 Q. Is it related to acetaminophen

17 or paracetamol at all?

18 MR. COHEN: If you can answer

19 that without violating any agreements,

20 go ahead. But if you think you might

21 be violating an agreement, then he

22 can't answer that.

23 A. I am not a hundred percent sure

24 if I can answer that question, so I would

25 prefer not to comment on it.

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1 MR. JANUSH: We're going to

2 mark this spot of the transcript for

3 further follow-up.

4 BY MR. JANUSH:

5 Q. You've received \$107,000 from

6 Haleon in connection with something called

7 Project HEP, part 2. What's that?

8 A. This is a -- what I can say

9 about it is that it's an extension, right?

10 Haleon was a company that split off of

11 GlaxoSmithKline, and that project is an

12 extension of the prior project with

13 GlaxoSmithKline. I'm under the same

14 contractual obligations not to discuss any

15 details.

16 Q. Does your contract ban you from

17 even confirming whether or not you are

18 studying acetaminophen?

19 A. As I said, I'm not a hundred

20 percent sure. I don't recall the exact

21 language of the contract. I don't feel

22 comfortable saying one way or the other.

23 I can say that it's not related

24 to the brain. I think I'm safe saying that.

25 Q. Haleon distributes

Page 380

1 acetaminophen products, right? Like Advil

2 Dual Action with acetaminophen and Panadol?

3 A. So my understanding is that

4 GlaxoSmithKline was a manufacturer of

5 acetaminophen in countries outside the US. I

6 don't recall -- I don't know exactly which

7 countries.

8 Since Haleon split off of that,

9 I don't know what -- exactly what Haleon's

10 relationship is to the manufacture of and

11 sales of acetaminophen.

12 MR. JANUSH: Can we take a

13 break?

14 MR. COHEN: Sure.

15 MR. JANUSH: Go off the record.

16 THE VIDEOGRAPHER: We are going

17 off record. The time is 5:30.

18 (Recess taken, 5:30 p.m. to

19 5:43 p.m. CDT)

20 THE VIDEOGRAPHER: We're going

21 back on record. The time is 5:43.

22 (Whereupon, Deposition

23 Exhibit P832, McGill Invoices, was

24 marked for identification.)

25 (Whereupon, Deposition

Page 381

1 Exhibit P832B, McGill Invoice, was

2 marked for identification.)

3 BY MR. JANUSH:

4 Q. Dr. McGill, I've premarked and

5 given you Exhibit P832 and P832B. These are

6 the invoices that we have from you to David

7 Cohen, counsel that's sitting across the

8 table from me, and Amy Ragone of Butler Snow.

9 They reflect billings from January 16, 2023

10 through September 4, 2023.

11 Have you had an opportunity to

12 review these billings?

13 A. Yes.

14 Q. Are these an accurate

15 representation of your invoicing from your

16 inception of expert work through the present

17 date?

18 A. They appear to be the

19 invoices -- copies of the invoices that I

20 submitted.

21 MR. JANUSH: Thank you,

22 Dr. McGill, for your time today. I

23 have no further questions.

24 THE WITNESS: Thank you very

25 much. I -- thanks, everybody.

<p style="text-align: right;">Page 382</p> <p>1 MR. COHEN: Do we need change 2 or can I just ask two questions? 3 (Technical comments off the 4 stenographic record.) 5 ----- 6 EXAMINATION 7 ----- 8 BY MR. COHEN: 9 Q. Just real quickly, Dr. McGill. 10 Earlier in the day, counsel 11 asked you about Exhibits 804, 805 and 806, 12 which are studies that are referenced in your 13 expert report on which you and Dr. Jaeschke 14 are coauthors, among others; is that correct? 15 A. I remember discussing the 16 articles. 17 Q. Okay. And it may have been 18 inadvertent, but counsel said, I think, that 19 these studies, which are cited in your expert 20 report, address the neurotoxic results of 21 acetaminophen. 22 Do you remember that? 23 A. If he made the statement, 24 then -- these are not studies of 25 neurotoxicity, so that would be inaccurate.</p>	<p style="text-align: right;">Page 384</p> <p>1 A. I do. 2 Q. And do you remember counsel 3 asked you about the conclusion and the 4 concluding sentence in the conclusion that's 5 cited in your expert report beginning with 6 the word "However, our findings suggest that 7 maternal use of acetaminophen at the 8 currently recommended dose is unlikely to 9 lead to accumulation of potentially toxic 10 levels in the fetus." 11 Do you remember that? 12 A. Yes. 13 Q. Can you point to -- or tell us 14 where the data are in the study that support 15 that statement? 16 A. Well, this statement is about 17 levels in the fetus, and they specifically 18 reference potentially toxic levels, and so if 19 we -- if we're talking about levels of 20 acetaminophen, the data are shown in Figure 1 21 so -- 22 Q. What does Figure 1 indicate, 23 briefly? 24 A. It's -- well, yeah. It's -- I 25 think -- I believe it's consistent with their</p>
<p style="text-align: right;">Page 383</p> <p>1 Q. And that was my question: If 2 he made that statement, was that an error? 3 MR. JANUSH: It was. 4 A. I feel like it must have been. 5 BY MR. COHEN: 6 Q. These studies do not address 7 neurotoxicity, do they? 8 A. No. 9 Q. Okay. And he also pointed out 10 that these studies indicate that McNeil, in 11 part, funded some of Dr. Jaeschke's work? 12 A. I believe that's what he was -- 13 yeah, suggesting. 14 Q. Do you remember that? 15 A. Uh-huh. 16 Q. Do the studies also indicate 17 that the NIH and other funding sources also 18 funded Dr. Jaeschke's laboratory? 19 A. I believe some of them 20 indicated that. I mean, he certainly 21 received funding from multiple other sources. 22 Q. You were asked earlier by 23 counsel about Exhibit 813, P813, which is the 24 Nitsche study from 2017. 25 Do you remember that?</p>	<p style="text-align: right;">Page 385</p> <p>1 statement there, and it indicates that 2 there's no accumulation or greater 3 concentration of acetaminophen in the fetus 4 than in the mother. So it's not reaching 5 toxic levels. 6 MR. COHEN: Okay. That's all 7 I've got. Thank you, Doctor. 8 THE WITNESS: Thank you. 9 MR. JANUSH: No further. 10 THE VIDEOGRAPHER: Okay. This 11 concludes today's deposition. We are 12 going off the record. The time is 13 5:48. 14 (Time noted: 5:48 p.m. CDT) 15 --o0o-- 16 17 18 19 20 21 22 23 24 25</p>

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1 CERTIFICATE

2 I, MICHAEL E. MILLER, Fellow of

3 the Academy of Professional Reporters,

4 Registered Diplomat Reporter, Certified

5 Realtime Reporter, Certified Court Reporter

6 and Notary Public, do hereby certify that

7 prior to the commencement of the examination,

8 MITCHELL R. MCGILL PhD was duly sworn by me

9 to testify to the truth, the whole truth and

10 nothing but the truth.

11 I DO FURTHER CERTIFY that the

12 foregoing is a verbatim transcript of the

13 testimony as taken stenographically by and

14 before me at the time, place and on the date

15 hereinbefore set forth, to the best of my

16 ability.

17 I DO FURTHER CERTIFY that pursuant

18 to FRCP Rule 30, signature of the witness was

19 not requested by the witness or other party

20 before the conclusion of the deposition.

21 I DO FURTHER CERTIFY that I am

22 neither a relative nor employee nor attorney

23 nor counsel of any of the parties to this

24 action, and that I am neither a relative nor

25 employee of such attorney or counsel, and

that I am not financially interested in the

action.

MICHAEL E. MILLER, FAPR, RDR, CRR
Fellow of the Academy of Professional Reporters
NCRA Registered Diplomat Reporter
NCRA Certified Realtime Reporter
Certified Court Reporter
Notary Public

Dated: September 11, 2023

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1 ERRATA

2 PAGE LINE CHANGE

3 _____

4 REASON: _____

5 _____

6 REASON: _____

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8 REASON: _____

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10 REASON: _____

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1 INSTRUCTIONS TO WITNESS

2 DATE: September 11, 2023

3 Please read your deposition over

4 carefully and make any necessary corrections.

5 You should state the reason in the

6 appropriate space on the errata sheet for any

7 corrections that are made.

8 After doing so, please sign the

9 errata sheet and date it.

10 You are signing same subject to

11 the changes you have noted on the errata

12 sheet, which will be attached to your

13 deposition.

14 It is imperative that you return

15 the original errata sheet to the deposing

16 attorney within thirty (30) days of receipt

17 of the deposition transcript by you. If you

18 fail to do so, the deposition transcript may

19 be deemed to be accurate and may be used in

20 court.

21

22

23

24

25

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1 ACKNOWLEDGMENT OF DEPONENT

2

3

4 I, MITCHELL R. MCGILL PhD, do

5 hereby certify that I have read the foregoing

6 pages and that the same is a correct

7 transcription of the answers given by me to

8 the questions therein propounded, except for

9 the corrections or changes in form or

10 substance, if any, noted in the attached

11 Errata Sheet.

12

13 MITCHELL R. MCGILL PhD _____ DATE _____

14

15 Subscribed and sworn to before me this

16 _____ day of _____, 20 ____.

17 My commission expires: _____

18

19 _____

20 Notary Public

21

22

23

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25

LAWYER'S NOTES

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